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PharmaED's

Impurities Forum 2009

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

MARCH 5-6, 2009, RADISSON-PLAZA WARWICK, PHILADELPHIA, PA

- **Examine FDA, ICH, and USP Approaches to the Control of Impurities**
- **Choose and Evaluate Tools for Impurities Identification**

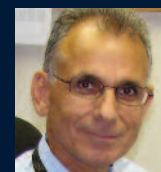
Plus: In-Depth Extractables and Leachables Coverage!

- **New Approaches toward the Identification of Extractable and Leachables**
- **Toxicology and Risk Assessment Considerations**
- **Extractable and Leachable Considerations for Photoinitiators**

Special In-Depth Session:

USP Approaches and Initiatives for Impurities

*Behnam Davani, Ph.D.,
United States Pharmacopeia (USP)*



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**Baxter Healthcare
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Thursday, March 5, 2009

8:30 *Chairperson's Welcome and Opening Remarks*

USP PERSPECTIVE

8:45 **USP Approaches and Initiatives for Impurities**
Behnam Davani, Ph.D., United States Pharmacopeia (USP)

Recent USP initiatives on impurities are to be presented. These include multiple impurity profiles in a drug substance using flexible monograph approach as well as policies relating to the use of the relative response factor to determine impurities. ICH and FDA approaches to the control of impurities as related to USP monographs are also discussed. The presentation will also provide highlights for the following related topics:

- Impurity definitions in USP and ICH
- Updates on General Chapters Residual Solvent <467>, Impurities in Official Articles <1086> and Heavy Metals <231>
- Acceptance limits for impurities in the USP monographs
- USP Monograph Redesign Initiative and Pending Standard monograph

About your session leader:

Dr. Davani joined USP in 1999 as the Scientific Manager for the USP Industry Outreach Program. In 2002, he accepted his present position as the Liaison to the USP Expert Committee for Monograph Development- Antiviral and Antimicrobial in the Small Molecules Department. He works with industry, FDA, and other scientific organizations to develop and revise monographs for drug substances and products.

10:45 *Refreshment Break*

11:00 **Challenges in Implementing USP <467> Residual Solvent Program**
Bill Zhu, Medication Delivery, Baxter Healthcare

The USP <467> became effective on July 1, 2008. Many pharmaceutical companies established programs to ensure compliance. However, the approaches different companies took varied greatly. The author intends to share his experience in establishing the residual solvent

program in Baxter Healthcare. The purpose of the presentation is to raise questions and facilitate thinking along these questions. The topics of the presentation include:

1. What residual solvents should one test?
2. What should be the residual solvent limits?
3. How does the USP residual solvent method work?
4. How to modify the USP method or develop one's own residual solvent method?
5. What headspace instruments to use?
6. What diluent should one choose?
7. Should the USP residual solvent reference standards be used?

11:45 *Luncheon*

REGULATORY CONSIDERATIONS

1:00 **FDA, ICH, and USP Approaches to the Control of Impurities**
Eric B. Sheinin, Ph.D., Sheinin & Associates
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 drugs not currently legally marketed in the U.S. The USP has revised 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?

CASE STUDY: IMPURITIES IDENTIFICATION

1:45 **It's a New Impurity! Isolating and Identifying Process Related Impurities in Drug Development**
Terri Natishan, Merck & Company
New impurities can appear suddenly in drug development due to changes in the synthetic process or quality of 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, chromatographic 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

2:30 *Refreshment Break*

2:45 **Impurity Considerations in Pre-Fillable Devices**

Justin M. Wright, PhD
Manager, Bio-Analytical Sciences
BD Medical - Pharmaceutical Systems

Current strategies for extractable/leachable programs are critical and necessary. However, for certain complex molecules and drug formulations, they may be too narrow in scope to provide adequate data and information for optimized container selection. Additionally, extractable/leachable studies are typically executed during the later stages of the development cycle when the risk for change becomes increasingly problematic.

As an alternative approach, BD has developed a robust strategy and program that ensures the highest probability of success in evaluating and choosing the most appropriate container at the earliest possible point in the development/ commercialization timeline. This science based approach will be presented along with case studies and the necessary capabilities needed for such a program.

3:30

Application of LC-MSn in Conjunction with Mechanism-based Stress Studies in the Elucidation of Drug Degradation Products and Degradation Pathways

Dr. Min Li, Manager,
Global Quality Services, Analytical Sciences,
Schering-Plough Corporation

ICH guidelines require that impurities of the active pharmaceutical ingredients (API) or key intermediates be identified and/or qualified once they exceed certain thresholds. The identification of these impurities/degradants can be quite challenging.

In this presentation, the use of LC-MSn technique in conjunction with mechanism-based stress studies is shown to be a very effective way in the elucidation of unknown drug degradation products and degradation pathways. Typically, samples are first analyzed using LC-MSn through which molecular ions, major fragments, and their structural relationship can be established. Based on these LC-MSn results, possible degradation mechanism may be inferred; a particular type of stress study (forced degradation) of the API is then designed and carried out accordingly. The formation of the degradant in the stress study is confirmed by LC-MSn through matching of retention times, UV spectra, and more importantly MS/MS fragmentation patterns between the stress-generated degradant and the one observed in the original sample. MS/MS fragmentation patterns generated with suitable collision energy not only provide a unique molecular fingerprinting in tracking and ensuring the targeted degradant be made in an adequate amount in the stress study but also reveal structural information critical to the elucidation of the degradant structure. With the elucidated structures of the degradant and its intermediates, degradation pathways can be proposed, which is essential for adequate formulation and packaging design to ensure suitable drug stability. This overall approach will be demonstrated through several case studies involving corticosteroid APIs.

5:00

Close of Day One

Friday, March 6, 2009

CASE STUDY PRESENTATION

8:30

Choose and Evaluate Tools for Impurities Identification**Paul Bigwarfe, Manager, ImpurID, Hospira, Inc.**

This session will be focused on what is needed to have a successful impurity identification effort. It is not sufficient to have the latest technology and instrumentation, but having the right personnel to design experiments and interpret the data is equally critical.

The latest instrumentation such as mass spectrometry, NMR, and chromatography systems will be discussed, with particular emphasis on their utility in impurity identification. Additionally, new software platforms that reduce data analysis time will be covered. Lastly, examples of impurity identification will be given that did not require advanced instrumentation, but instead were solved with basic chemistry and the know-how of the scientists involved. Both sides of the issue will be tied together by wading through the steps involved in an impurity identification project.

- Learn about the latest in instrumentation for impurity identification
- Discover how with the right scientific approach, basic chemistry can solve impurity ID issues
- Hear real-world examples of how an impurity was identified and the root cause determined.
- See how both the right people and the right instrumentation are required for a successful impurity identification team.

EXTRACTABLES AND LEACHABLES

9:15

Toxicology Issues in Extractable 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.

10:00

A Strategy for Determining Leachables in Liquid Drug Products**Jim Castner, Ph.D., Sr. Principal Research Scientist, Lantheus Medical Imaging**

The most commonly used analytical technique for determining impurities in liquid drug products is HPLC, which has a primary focus on monitoring stability indicating compounds associated with the drug substance. Besides detecting and quantitatively monitoring formulation impurities, the same HPLC method also has the potential for determining leachables in the tested product. The ability of one analytical method to provide information about the stability of the pharmaceutical plus product compatibility data, related to exposure to manufacturing equipment and primary packaging material, affords a significant economy of analytical resources for the pharmaceutical industry.

In this presentation, method development techniques will be presented for expanding the analytical capability of HPLC procedures to detect both drug substance impurities and leachables. These techniques are based upon the use of multiple detection systems coupled with an assessment of chromatographic resolution capability. This assessment is achieved by using a

series of reference compounds, which have distinct partition or distribution properties, to calibrate the chromatographic range for a given method. Several examples will be given to demonstrate the application of these techniques as well as its limitations.

10:45 **Strategies for Identifying Leachables in Protein-based Large-Volume Parenterals**

Parth Sampathkumar, Quality Scientist, Sangart, Inc

Investigating extractables and leachables (E&L) of pharmaceutical containers is a regulatory requirement. The regulations and industry guidelines require that changes in the quality of the product that may occur due to the interactions between the formulated biotechnological/biological product and container/closure be reported and the effects determined. However, these E&L studies require careful planning, development of analytical methods and methods validation, long-term stability commitments and a big budget. An all encompassing E&L program is therefore often initially met with little enthusiasm by management.

This presentation will focus on protein-based large-volume parenterals and attempt to:

- Provide a cost-effective model E&L strategy
- Methods to qualify the immediate product storage container, and
- Identify Leachables during the course of stability studies

11:45 **Luncheon**

1:00 **Leachable Study on Solid Dosage Form**

Xueguang Fang, Scientific Fellow, Merck & Company

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-methylpropionone, 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.

1:45 **A New Approach for the Identification of Impurities, Extractable, and Leachables Utilizing Unit Resolution GC and LC Quadrupole MS**

Yongdong Wang, Don Kuehl Vice President, Marketing and Product Development, Cerno Bioscience

The ability to provide formula identification of unknowns via mass spectrometry is a powerful tool to assist in the identification of impurities, extractables, and leachables. GC/MS depends on library searches to identify unknowns but search results can sometimes be ambiguous, or in the case where the unknown is not present in the library, incorrect, misleading, or inconclusive. LC/MS does not provide the unique fragmentation patterns for compound ID and at best provides confirmatory information by nominal mass. LC/MS/MS provides a richer set of nominal mass values but automated library searches are not available and instead careful interpretation of the data is required. Accurate mass instruments can provide more precise, although rarely unique, formula ID for the molecular ions or their fragments. This information can provide complementary and confirmatory information in conjunction with other techniques to improve the speed, confidence, and accuracy of unknown identification. Unfortunately, these instruments are substantially more expensive, more difficult to operate, and typically require highly trained operators to be most effective.

Recent advances in MS instrument calibration methods has enabled typical bench top quadrupole GC and LC/MS systems to provide substantially improved accurate mass information, and perhaps even more importantly, accurate peak shape information. The well defined peak shape information dramatically improves the ability of these class instruments to perform very accurate formula

ID by virtue of the ability to match the unique isotope pattern of the ion formula in conjunction with the accurate mass. This approach can be easily performed using existing GC and LC/MS instrumentation without the need for any additional hardware, only a simple calibration procedure is required. This new approach of performing formula ID on unit resolution MS is well suited to assist in the rapid and accurate identification of impurities, extractables, and leachables and some sample applications using both GC and LC/MS shall be illustrated.

- Utilize your existing GC or LC/MS quadrupole instruments to provide accurate formula ID to speed up analysis time and improve confidence in results
- Provide additional confirmatory information in support of GC/MS search results to minimize misidentification
- Identify ion fragment formula from GC/MS or daughter ions from MS/MS to aid ID quickly and simply without the need for expensive and complex high resolution accurate mass instruments.

2:30

Methods for the Identification of Leachables and Extractables

James R. Scull, Ph.D., Executive Director & Managing Member, Pharmalytica Services, LLC

Extractable are chemicals that are extracted under controlled conditions from the container, closure system or other packaging components. When these compounds migrate or leach into the drug product over time, they are called leachables. These substances have the potential to contaminate the drug product in a detrimental way. Testing for extractables and leachables is an area which is receiving much focus from the FDA. Much is unknown about this type of study and minimal guidance is available.

This presentation will discuss the methods, techniques and instrumentation employed throughout an extractable and leachable study. We will follow a study from the beginning stages of the controlled extractions through the identifications, method development and validation to the final migration study. Throughout these stages we will focus on the strengths and weaknesses of the various techniques and methods as well as some obstacles that were encountered along the way.

3:15

Refreshment Break

3:30

Strategies for Investigating and Identifying Extractable

Andrea Straka, Manager, West Analytical Services

A thorough investigation of a drug product for leachables must begin with a complete understanding of the extractables profile of the packaging materials. By definition, extractables are chemical species that migrate from materials when placed under stressed conditions. Those stressed conditions are created in controlled laboratory experiments. This session will cover:

- The reasons why extractables testing is essential to a successful leachables study
- Techniques for the assessment of extractables
- Strategies for working with material suppliers to identify unknowns
- How understanding package extractables can contribute to a QbD approach to pharmaceutical development

CLOSURE SYSTEMS

4:15

The Use of Extractable/Leachable Testing for Qualification of Disposable Components and Closure Systems

Steve Doherty, TOXICON

As regulatory agencies become more aware of and concerned with drug impurities in drug formulation, the need for comprehensive material evaluation has become more critical. Extractable and leachable compounds may be introduced by a number of components during the manufacturing and storage of drug products; these include tubing, gaskets, containers, filters, closures, etc. A properly designed program will allow for the evaluation of a various component types using a comprehensive analytical analysis to understand the material(s) and their potential interactions. This study can be used to mitigate the risk to patient and provide support for a successful regulatory submission. Strategies for the design and execution of a qualification program will be discussed to allow for the implantation of appropriate materials to allow for the full advantages of disposables to be realized, while minimizing potential downstream contamination. Key points will include:

- Points of consideration in designing a study
- An overview of suggested analytical techniques
- Examples of surprising results from E&L studies

5:00

Close of conference



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