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# Container Closure Systems

*Strategies for Selection, Compliance, and Mitigation  
of Extractables and Leachables Challenges*

JANUARY 25-26, 2010, RADISSON-PLAZA WARWICK, PHILADELPHIA, PA

## Key Learning Objectives:

- Understanding the Unique Container Closure System Considerations and Requirements for Various Drug Products
- Determining the Presence of Extractables and Leachables
- Understanding Testing Requirements for Container Closure Systems
- Evaluating and Selecting Materials for Container Closure Systems
- Developing Internal Quality Control Programs For Container Closure Systems
- Innovations in Container Closure Systems and New Industry Technologies

## Special In-Depth Session:

### Evaluating and Selecting Polymeric Materials for Container Closure Systems

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

## Featuring Representation From:

BD Medical Pharmaceutical Systems

Eli Lilly & Company

Hyaluron

Material Needs Consulting, LLC

Packaging Science Resources, Inc.

West Pharmaceuticals

Eakins & Associates

Helvoet Pharmaceuticals

Linda A. Walker Consulting, LLC

NAMSA

Phase Technologies, Inc.

Whitehouse Analytical Laboratories, LLC



**PharmaED**  
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Monday, January 25, 2010

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

## MATERIALS EVALUATIONS

8:45 **Evaluating and Selecting Polymeric Materials for Container Closure Systems**

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

When developing new drug products, two goals should always be kept in mind: speed to market and sustainability. Selecting the proper components for the container closure system can greatly impact both of these goals. Understanding the global regulatory requirements for these components is essential. Developing a well thought out and efficient testing program to ensure patient safety and drug product compatibility can affect the time required for the overall product development as well as influence its long-term performance. Too much testing can cost valuable time and money, however, too little may result in oversights in some of the key safety and performance issues for the packaging, resulting in amendments in regulatory submissions or worse, product recalls.

Many of the components used in today's pharmaceutical packaging, both primary and secondary, are fabricated for polymers. Plastic and elastomers (rubber) are replacing the more traditional materials, such as glass and metal, because they are light weight, flexible, and in many cases more durable than their counterparts. However, due to their composition and need for additives to provide the required stability and enhanced effects, polymers are also more prone to releasing leachables into the drug products. It is, therefore, very important to understand their formulation and the inherent risks associated with each chemical species used in their composition. This burden is often shared by both the pharmaceutical company and their suppliers with regard to testing as well as some of the regulatory submissions. It is crucial that these entities work together and understand the regulatory requirements for these container closure system components and who is ensuring that they are met. The ultimate responsibility rests with the pharmaceutical company that is marketing the product, but in today's economy, there is a great deal of push-back to the vendors to provide some of the testing data. It is very important for the pharmaceutical company to understand the true meaning of the information supplied by the vendor. For example, is the material approved for food contact application by a regulatory authority or does it only have a letter of opinion from a consulting group indicating its safety? Is it listed on the EU Pharmacopeia? The answers to these questions can impact the speed and sustainability goals mentioned above. The vendors can also benefit from this working

relationship with their pharmaceutical customers by becoming a "Vendor of Choice" and providing the necessary information and guarantees for their products that will ensure speed and sustainability for the client.

This short course will provide an overview of the issues associated with the use of plastics and elastomers for container closure systems, insights on the global regulations impacting these materials, and recommendations for evaluating the needs of the pharmaceutical product and selecting the most suitable materials to meet these requirements. Topics covered will include:

- An introduction to polymer degradation and stabilization
- Selecting the best polymers, stabilizers, and colorants to meet the packaging requirements
- Understanding the global regulations required for container closure systems components taking into account product forms and routes of entry
- Best practices for Extractables and Leachables testing programs
- Typical extractables profiles for the materials used in container closure systems
- The polymer supply chain and sources of unexpected leachables
- Partnering with vendors and becoming a "Vendor of Choice"
- Considerations for minimizing the risk of materials selection and streamlining the testing required for container closure systems made from these sources

10:15 *Refreshment break*

10:30 **Evaluating and Selecting Materials for Container Closure Systems**

*Eugene T. Polini, III, Customer Technical Support Representative, WEST*

This segment will be a discussion of the process by which elastomeric recommendations for new products are made. Topics to be discussed will be the product recommendation process, prescreening process, materials of construction, films and coatings, and post treatments. By understanding the material properties and chemistry of primary packaging materials pharmaceutical scientists can be better positioned for success in this increasingly competitive landscape.

11:15 **Application of a Risk-based Approach in the Development and Use of a Monitoring System in a Pharmaceutical Rubber Manufacturing Plant**

*Lisa Marie Yoest, Technical Support Manager, Helvoet Pharma*

Risk based approach was introduced by the FDA in Sept 2004 "Pharmaceutical cGMPs for the 21st Century – A risk based approach – final report" and by the ISO 15378 in March 2006: "Primary packaging in medicinal products –

particular requirement for the application of ISO 9001:2000, with reference to GMP”.

By these standards, manufacturers of packaging materials for the pharmaceutical industry are encouraged to include an effective management of the risks associated with the design, development and manufacturing of primary packaging materials.

For the introduction of the next FirstLine™ concept, Helvoet Pharma has taken the opportunity to implement the risk-based approach. All systems used during the manufacturing of a rubber component have been assessed by performing a FMEA (Failure Mode and Effect Analysis) : risks are identified per system and evaluated for probability and severity. This results in a risk number. For all elements with a high risk number, an inherent safety by design is preferred. However, this is not always possible. The second option in risk controlling is to implement a measuring system to detect the weaknesses. This will enable to act already during processing of the goods. The last option is to control residual risk by SOP's, In- Process Control and final inspection.

The monitoring system implemented by Helvoet Pharma will be controlling the critical process parameters that can have a direct impact on the product quality. All measurements and alarms will be stored and available for further assessment. The system will be validated using FDA's Part 11 principles.

12:00 Luncheon

## MATERIALS EVALUATIONS

1:30 **Pharmacopeial Control of Container Materials, Container Accessories and Container-Closure Systems**

*Dr. Michael N. Eakins, Principal Consultant, Eakins & Associates*

The USP and the European Pharmacopoeia (EP) contain chapters on materials for the construction of pharmaceutical containers, pharmaceutical containers, elastomers and lubrication aids. There has been some movement in recent years in bringing the USP and EP chapters closer in their requirements but there are still differences. The presentation will review the current situation for glass, plastic and elastomers in the two pharmacopeias and discuss possible future revisions in the USP chapters. The presentation will also discuss USP's requirements for container performance testing (moisture permeation through plastic containers) and the proposed USP chapter on pharmaceutical coil.

2:15 **Container Closure Testing – Beyond the USP**  
*Linda A. Walker, President, Linda A. Walker Consulting, LLC.*

USP testing is mandatory for most container/closure systems, but does it tell you enough? Other organizations have created test methods, including ASTM D10 and F2, IATA/ICAO, and DOT, but what will tell you what you want to know? How can you apply testing methodologies in sequence or concurrent combinations to provide a better picture of what is and isn't working and what it takes to make your primary container fail.

When you experience field failures or problems with a primary container/closure system, often no obvious cause, package engineers must do some creative problem solving. Recognized standard tests can help bring frame the cause, or causes, of the failure. Once you determine HOW the package failure occurred, you can determine the best course of action and implement effective change in the most cost effective, and efficacious fashion.

3:00 Refreshment Break

## CASE STUDIES

3:15 **Innovations in Container Closure Systems and New Industry Technologies**  
*Tibor Hlobik, Associate Director, Marketing for PFS Technologies, WEST*

There continues to be strong market growth in injectable therapeutics, primarily driven by biological proteins and vaccines. As a result novel innovative drug packaging presentations are available and being developed for improved drug-package stability, to eliminate silicone oil and tungsten known to cause protein aggregation in pre-fillable syringes and to be suitable for low temperature storage conditions.

Understanding primary packaging material options and selecting optimum container closure systems for lifecycle containment is important to minimize risk and development costs. This discussion will cover and include case examples in support of:

- Standards and selection for vial and prefillable syringe components
- Solutions for sensitive biotech drug products
- Functionality considerations for delivery systems
- Combination products for market differentiation and improved compliance

4:00

## Container Closure for Parenteral Products- Integrity by Design

*Dr. Mihaela Simianu, Eli Lilly & Company*

The container closure system is an intrinsic part of the parenteral product and essential to delivery and handling of the pharmaceutical product. It defines the closure, protection and functionality of a container while it ensures the safety and quality of the drug product over the product shelf life. Integrity of a container must be ensured during parenteral product development, manufacturing and product shelf life. Integrity is assured both by the design and the fit between container/closure components and well as the process used for its assembly. Computer modeling and analysis may be used to understand and control the variation of the attributes for each component of the container closure used to create the closure fit. Testing for integrity using new technologies at line or in line with filling/sealing operations may be performed using computer controlled systems. This presentation will discuss application of such tools for parenteral products in vials. Applicability can be extended to other systems

### Rationale

The implementation of change and the continuous improvement of primary packaging components are an important source of projects and activities to be appropriately managed at a manufacturing site. The presentation will provide case studies and models, which may be used to effectively introduce local and global changes to the container closure components in contact with parenteral products and ensure their integrity by using computers for data analysis and modeling. The models can be applied to improve the materials process, update definition of components quality with suppliers, update components specifications and control strategies as needed to maintain product quality and the validation state of the container closure systems.

4:45

*Close of Day One*

**Tuesday, January 26, 2010**

8:45

## A Rapid Nondestructive PAT Method for Determining the Moisture Content in Elastomer Closures

*Dr. Thomas A. Jennings, Phase Technologies, Inc.*

This presentation will describe how a measure of the dielectric properties of an elastomer closure can be used to rapidly (in seconds) estimate the free moisture content.

The first part will give a general description of the apparatus and a brief description of the key dielectric properties that will be measured, i.e., Quality Factor (Q) and the capacitance (Cp). The method used for correlating the Q value to the free moisture content in a test lot of 32 closures by gravimetrically determining loss in weight as a result of drying at 100oC will be described.

Correlation data between the  $|Q_{avg}|$  and  $M_i/|Q|$  for both 20 mm and 13mm closures will be presented. Data will be shown indicating that the bound moisture in closures is formed during the steam sterilization process. Tables will be shown that list the average moisture content determined for ninety 20 mm and one hundred and forty seven 13 mm closures. Histograms for both gravimetric measured losses in weight will show a bimodal distribution of moisture in the closures. Use of this PAT method for the rapid and nondestructive measurement of moisture in closures will be listed.

## EXTRACTABLES & LEACHABLES

9:30

### Extractables and Leachables: Case Studies That Demonstrate How the Pharmaceutical Industry is Managing the Process of Identifying, Measuring, and Qualifying

*Edward J. Smith, Ph.D., Principal Consultant, Packaging Science Resources*

Ever since the FDA Packaging Guidance was issued in 1999, interest in extractables and leachables (E&L) issues has grown at a very rapid rate. This is evidenced by the significant number of courses and conferences on the subject held each year. The management of E&L from container-closure systems (CCS) has become a necessary part of the development and marketing of any new drug product. Although the primary goal of any E&L management program is to mitigate risk to the patient, the currently available guidances are not always specific regarding the precise steps to take in this process. This presentation will discuss the available guidances and regulations, sources of extractables and leachables from both packaging and process materials, and methods of identifying, measuring, and qualifying leachables for specific drug applications. In doing so, the work of the Product Quality Research Institute (PQRI) on inhalation, ophthalmic, and parenteral products will be reviewed. Finally, case studies will be reviewed from both packaging and process materials applications to demonstrate how E&L issues can be managed. Examples will also be discussed to show how E&L can be reduced through the judicious choice of contact materials.

11:30 **Rubber Extractables & Leachables: From Screening to Identification**

*Vincent Laperle, Analytical Manager, BD Medical – Pharmaceutical Systems*

BD offers quality products to enable pharmaceutical customers succeed in drug development using prefillable syringes as primary packaging. To support our customers, BD ensures the drug delivery system functionality, providing consultative expertise to help customers quickly and easily choose the most suitable container system including rubber components. In addition, BD is offering specific services such as Extractables and Leachables tests to help customers address regulatory requirement. This presentation will exchange a strategy on how to perform Rubber Extractables and Leachables study, and how to achieve identification of unknown peak with appropriate analytic tools.

12:00 *Luncheon*

1:30 **The Process of Determining the Presence of Extractables and Leachables**

*Harmony Sy, Technical Specialist/Lead chemist, Research and Development Department, NAMSA*

There is an increased focus on what compounds extract from container/closure materials and what leaches from the container closure system. This presentation will explain the process of the extractable and leachable profiles focusing on the analytical method development and validation process.

An extractables profile is needed to accurately choose compounds that will extract and could possibly leach from the container into the material. A toxicological assessment should be performed to evaluate these profile results. There should be collaboration between the chemist, client, and the toxicologist with the choosing of the compounds for the method validation. The development and validation of the methods for the leachable testing must be conducted using the recognized guidelines such as International Conference on Harmonization (ICH) and United States Pharmacopeia (USP). Once the method is validated, the leachables profile is performed.

- Provide a step by step process from the extractables profile through method development and the leachables profile
- Explain the process of developing and validating an analytical method
- Provide real-life examples of what problems occur during a method development

## DEVELOPMENT CASE STUDIES

2:15 **Comparison of CCI of Syringes vs. Vials During Transport**

*Shawn Kinney, President, Hyaluron*

It has been shown that during air transport of pre-filled syringes, the stoppers are prone to move in response to changes in ambient pressure. This puts in question the container closure integrity of syringes exposed to reduced pressure. A syringe stopper may move back under reduced pressure and possibly pull contaminants back into the product as the stopper returns to its original position when the reduced pressure is removed. This phenomenon is not observed with vials since the stopper is held in place. This might suggest that a vial is a more rugged container under reduced pressure than a syringe. In this study we demonstrate that with appropriate control over the gas headspace in a syringe the stopper movement can be reduced to negligible. Further we show that if a true CCI failure (i.e. small hole in a stopper, crack in the container, or other defect that creates a path to the outside environment) exists a syringe is a better container to prevent contamination than is a vial.

3:00 **USP Container Testing Requirement: Revisions, Confusion and Reality**

*Brian Mulhall, Chief Operations Officer, Whitehouse Analytical Laboratories, LLC*

The container testing requirements as outlined by the USP have been a major point of discussion over the past few years. USP container test chapters that for years endured no substantial revisions underwent a confusing and poorly communicated major revision in December 2007. Since then, additional calls for improvement by industry have been voiced and these chapters continue to be ever so slightly altered on a supplement by supplement basis. Has anything really changed? Has this process lead to more effective and improved test procedures? This presentation will review the multiple revisions and suggestions for revision that have taken place over the past few years and provide the audience with direct insight as to what the current requirements are, where they are heading and ways they can be improved. Audience members will be able to walk away with a real time understanding of their package testing obligations.

4:00 *End of Conference*



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