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PharmaED's

Container Closure Systems

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

NOVEMBER 11-12, 2010, RADISSON WARWICK HOTEL, PHILADELPHIA, PA

Key Learning Objectives:

- Selecting and Evaluating Materials for Container Closure Systems
- Reducing the Potential for Interaction Between Dosage and Components of Container Closure Systems
- Assessing the Influence of Container Closure Systems on Drug Stability
- Pharmacopeial Control of Plastic Materials for Containers
- How Custom and Semi-Custom Packages Can Reduce QC and Production Costs and Timing
- Satisfying Evolving Quality Expectations for Glass Injectable Packaging
- Determination of Extractables and Leachables for Container Closure Systems
- Extractables and Leachables Case Studies

Special Expanded Session:

Evaluating and Selecting Polymeric Materials for Container Closure Systems

Featuring Representation From:

Genzyme Corporation
Material Needs Consulting, LLC
West Pharmaceutical Services
Chemic Laboratories, Inc.
Pharmalytica Services
Kiang Consultant Services
Eakins & Associates
SCHOTT forma vitrum
Toxikon Corporation
Pfizer, Inc.
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Thursday, November 11, 2010

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

8:45 **Reducing the Potential for Interaction Between Dosage and Components of Container Closure Systems**

Patty Kiang, PhD,
Kiang Consultant Services

Container closure system is an integral part of the drug product; it provides the protection from light, temperature change, vibration and microbial contamination. It provides the shelf life of the drug product. There are 4 major mechanisms of interactions between container closure system and drug product. They are permeation, adsorption, absorption and leaching. In order to reduce or eliminate the interactions, the following items will be discussed:

1. Component material selection
2. Barrier coating
3. Container closure design
4. Process modification

9:30 **Assessing the Influence of Container Closure Systems on Drug Stability**

Abizer Harianawala, Ph.D., Senior Scientist (Formulations), Genzyme Corporation, Drug and Biomaterials R&D

The container closure system plays a significant role in protecting the pharmaceutical dosage form from degradation caused by potential physical, chemical and microbiological factors. The degradation products could significantly affect the safety and quality of the drug product leading to a reduction in shelf life and a significant increase in development costs and time for commercialization.

The presentation will cover:

- Potential factors affecting stability of drugs in oral solid and parenteral dosage forms
- Selection and testing of the commonly used container closure systems
- regulatory guidances
- Child resistant requirements
- Application of Quality by design approach
- Use of predictive models
- Case study review

10:15 *Refreshment break and exhibit viewing*

EXPANDED IN-DEPTH SESSION!

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

Michael A. Ruberto, President, 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 presentation 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

12:00 *Luncheon*

1:30

Pharmacopeial Control of Plastic Materials for Containers

Michael N. Eakins, Ph.D., Principal Consultant, Eakins & Associates

The USP and European Pharmacopeia have different approaches to the control of plastic materials used for containers and for plastic containers themselves. The presentation will review the current position of the JP, EP and USP and evaluate how the USP can update chapter <661> Containers-Plastics to make it more relevant to plastics that are widely used to package both solids and parenteral products.

2:15

Selecting and Evaluating Materials for Container Closure Systems

Andrea Straka, Technical Account Specialist, West Pharmaceutical Services

Over the last two decades, drug formulations have become more complex and container closure systems have become more sophisticated to meet those growing needs. These complexities no longer allow just any container closure to be plucked from a drawer and used with the drug product. What worked in the past may not be the best selection for today's drugs. Also, assembling Also, assembling the CMC section of a regulatory filing requires building a body of data and information to prove a scientifically sound selection of a container closure system or device has been made. This session will:

- Review examples of issues and market recalls due to poor selection of CCS materials
- Discuss strategies for selecting a container closure system that is "suitable for its intended use"
- Present solutions for evaluating container closure integrity and material/drug compatibility

3:00 *Refreshment Break*

3:15

Better Quality Built In: How Custom and Semi-Custom Packages Can Reduce QC and Production Costs and Timing

Linda Walker, President, CCM Specialists

During this presentation, we will review a case study of custom tools and specifications in partnership with vendors to statistically control component production to streamline the product production process. Working in partnership with vendors on custom designs or dedicated tooling of common designs can provide significant benefits over many years:

1. Do the work up front
2. Virtually eliminate incoming component QC for material release
3. Reduce labor hours and turn around time for component release
4. Maintain container/closure system torques within specification to meet CPSC child-resistant requirements
5. Reduce high speed line problems in the filling and packaging operations.

These same principles can be applied to stock sizes when tooling and manufacturing process are properly controlled. Finding vendors that do the job right can save headaches, lost time, re-work, and production problems in the filling/packaging operation and improve customer satisfaction.

4:00

Case Study: Satisfying Evolving Quality Expectations for Glass Injectable Packaging

Howard Drake, Vice-President, Ompi of America

The stringent quality requirements defined by the Pharma industry for glass containers are driving the development of new and complex inspection systems. The idea of a glass container being just a tool containing a substance for its distribution is now substituted by the concept of an individual packaging where the quality aspect is a key factor impacting the perception of the drug. Process development must take into account the final quality requirements to design a lean and smooth process including, from the very beginning, the most sophisticated inspection devices. This presentation will illustrate a successful case based on redesigning the manufacturing process combining experiences in a Japanese quality approach:

- Glass forming knowledge
- Integrated dimensional and inspection control
- Production fully in a controlled environment

4:45 *Close of Day One*

Friday, November 12, 2010

EXTRACTABLES & LEACHABLES COVERAGE

8:45

Determination of Extractables and Leachables for Container Closure Systems

Neil Pothier Ph.D., Chemic Laboratories, Inc.

Determination of extractables and leachables in container closure systems can be a challenge to any pharmaceutical, Biotech or medical device organization. This presentation will highlight a variety of container closure systems used to contain and/or deliver final drug product. A series of case studies will illustrate the need for well-designed Extractable and Leachable programs that are appropriate for the container closure system and drug product.

- The criticality of understanding the study sponsor's program and timelines
- The importance of sharing manufacturer, study sponsor and contract laboratory information and expertise
- Regulatory implications and potential pitfalls for each study program will be addressed
- Case #1: A controlled extraction study for a serum stopper and vial container closure system used to contain an injectable drug product will be outlined for the determination of extractables
- Case #2: Leachable investigation inclusive of method development, validation and stability testing of extractables identified in case #1
- Case #3: Study Sponsor receives change control notification from Metered Dose Inhaler (MDI) manufacturer that the drug delivery device is undergoing a material change. How do we ensure the extractable profile has not changed and who is responsible for conducting the assessment? Routine extractable testing indicates no change in extractable concentration for one analyte and method. However, a second extractable method indicates the presence of new extractable peaks!
- Case #4: The steps involved in developing, validating and performing stability testing for the presence of new extractables as potential leachables identified in case #3

9:30

Building Efficiencies in Extractables/Leachables Testing

Mary Schafer, Scientist, Pfizer, Inc.

Companies are always looking for ways to shorten timelines and reduce cost. Yet, to comply with the regulatory guidances related to extractables and leachables, the testing can be quite time consuming and expensive. This presentation will outline an approach that has been proven to reduce time and cost while fulfilling the current regulatory expectations. Platform studies assess the controlled extractables profiles of multiple components in one study, permitting side-by-side comparisons, thus leading to informed selection of packaging materials and subsequent progression directly into leachables studies.

10:15 *Refreshment break*

10:30

Extractable/Leachable Testing in Quality Control Programs: Testing Strategies and Lessons for a Successful Outsourcing Partnership

Stephen Doherty, Ph.D., Technical Manager, Extractable/Leachable Program, Toxikon Corp.

This presentation will look at two different aspects of material testing. The first aspect will focus on testing strategies for material evaluation and the second aspect will focus on working with a CRO to conduct testing. The assurance of the purity of a product begins with the raw materials. Extractable and leachable testing can be used as a component of quality control activities. Testing can range from evaluation of incoming material to stability samples to final product testing. Early testing allows for product quality and the early detection and remediation of the introduction of potential impurities. Such testing may be conducted in-house or outsourced to a CRO. The use of a CRO can be an effective way to augment internal capabilities, access subject expertise/experience, achieve cost benefits and provide efficient means of meeting project deadlines, while also presenting unique challenges. The key to a successful relationship is to align the expectations, deliverables and processes early on to ensure that the expectations of all parties are met. Strategies for facilitating a successful relationship, responsibilities for both sides and pitfall to avoid, will be discussed.

- Points of consideration in designing a study
- An overview of suggested analytical techniques
- Outsourcing considerations
- Strategies for a successful relationship
- Understanding responsibilities

11:15

Application of Quality by Design (QbD) Principles to Extractables/Leachables Assessment: Establishing a Design Space for Terminally Sterilized Aqueous Drug Products Storedin Plastic Packaging System

Dennis Jenke, Ph.D, Principal Scientist, Physical and Chemical Sciences, Baxter Technology Resources

The concept of Quality by Design (QbD) reflects the current global regulatorythinking related to pharmaceutical products. A cornerstone of the QbD paradigmis the concept of a design space, where the design space is a multidimensionalcombination of input variables and process parameters that have beendemonstrated to provide the assurance of product quality. If a design space canbe established for a pharmaceutical process or product, then operation within thedesign space confirms that the product or process output possess the requiredquality attributes. This concept of design space can be applied to the safety(leachables) assessment of drug products manufactured and stored in packagingsystems. Critical variables in such a design space would include thosevariables that impact the interaction of the drug product and its packaging, including (a) composition of the drug product, (b) composition of the packagingsystem, (c) configuration of the packaging system and (d) the conditions ofcontact.
This presentation proposes and justifies such a leachables design space foraqueous drug products packaged in

a specific plastic packaging system. Such adesign space has the following "boundaries":

- Aqueous drug products whose pH is inthe range of 2 to 8 and which contain no polarity impacting agents such asorganic solubilizers and stabilizers (addressing variable a).
- Packaging systems manufactured frommaterials that meet the system's existing material specifications (addressingvariable b).
- Nominal fill volumes from 50 mL to1000 mL (addressing variable c).
- Products subjected to terminalsterilization and then stored at room temperatures for a period of up to 24 months (addressing variable d).

The ramification of such a design space is that any drug product that fallswithin these boundaries is deemed to be compatible with the packaging system,from the perspective of safety, without the requirement of supporting drug-product testing.

12:00 *Luncheon*

EXTRACTABLES AND LEACHABLES CASE STUDIES!

1:15 **A Case Study on the Forced Extraction Study of a Sample Container Closure System and the Evaluation of the Leachables into the Topical Solution Drug Product Formulation**

Kurt Moyer, Director, Analytical and Bioanalysis, Pharmalytica Services

A controlled extraction study of a container closure system consisting of an HDPE bottle, an LDPE closure and a printed label was done. For the volatile and semi-volatile extractables, 49 of 50 observed extractables were identified. For the nonvolatile extractables, only 1 of the 14 extractables observed was identified. A headspace GC-FID and a HPLC-UV method were developed and validated for leachables in the drug product. Samples from the 25ºC/65%RH stability study were submitted starting at the 3-month pull for leachables analysis. For the first 9 months, no leachables or unknowns were observed at or above the AET. After 12 months, a volatile unknown was detected above the AET by the headspace GC-FID method. This unknown was confirmed by mass spec and retention time match to a reference standard to be the leachable cyclohexane. Cyclohexane was observed in all following stability time points. After 18 months, four non-volatile unknowns above the AET were detected by the HPLC-UV method. The unknowns were proven from LC-MS analysis to be degradation products of the active pharmaceutical ingredient and were not leachables.

2:00 **Case Study: Extractables Study on the Innovative Injentle TM Syringe System**

Horst Koller, Regulatory Affairs and Quality R&D PP, SCHOTT forma vitrum

- Purpose of Study
- Methods of Analyses
- Results and Conclusion of Extractable Study

2:45 **Novel Peroxide Curable Butyl Rubber with White Fillers**

L. Ferrari & L. Knight, Senior Scientists ,Global Research & Development, LANXESS Inc.

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 Butyl elastomer, a copolymer of isobutylene with approximately 2 mole % of isoprene is manufactured commercially via carbocationic polymerization. Due to its good balance between flexibility and barrier properties, butyl rubber is an important synthetic elastomer. To increase the crosslinking reactivity and co-compatibility of butyl rubber with other highly unsaturated elastomers, brominated and chlorinated butyl elastomers were developed. Conventionally, regular and halogenated butyl rubber are cross-linked with sulfur and/or zinc complexes, resins or amines to produce molded articles, such as tires. Traditionally, it was believed that regular butyl rubber could not undergo peroxide crosslinking, because polymer degradation would occur instead. LANXESS has developed a new technology to produce butyl elastomers containing up to 8 mole % of isoprene. Due to the increased isoprene level in the butyl rubber, these elastomer formulations can now include peroxides as a means to cure regular butyl rubber. Benefits derived from using peroxides as a curative include:

- Cleaner cure system
- Does not contain halogens, heavy metals or sulfur by-products
- Faster throughput for compression molding
- Excellent compression set properties for pharmaceutical closures

Results highlighting the use of various peroxides and co-agents with white-filled high isoprene butyl rubber compounds will be presented.

3:30 **To Change or Not to Change: E&L Support for Container Closure Systems Change Control**

Martha Gill, Research Scientist, Baxter Healthcare Corporation

Container Closure Systems are rigorously characterized with respect to their potential to interact with their contained therapeutic product as well as with respect to their safety. This characterization is time consuming and expensive, but must be performed as part of the regulatory submission package for the container closure system. It is an unfortunate condition of the medical plastics industry that the composition of packaging materials is in constant flux due to economic factors or to changes made by the material supplier. This talk describes a strategy for managing change control from the Extractables and Leachables perspective and presents a case study of the procedure used to support a material change to an approved container closure system.

4:15 **Panel Discussion**

5:00 *End of Conference*

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