

PharmaEd's

# 7<sup>th</sup> Annual Pre-Filled Syringes Forum

Strategic Development, Safety & Regulatory Compliance, and  
Commercialization of Pre-Filled Syringes  
May 19-20, 2014, Racquet Club of Philadelphia, PA

## Featuring Lessons Learned and Case Studies From Industry Experts:



- **Pre-Filled Syringe Manufacturing: A Review of Processes and Challenges**  
- *Gregory A. Sacha, Senior Research Scientist, Baxter BioPharma Solutions*

- **Linking Technology with Patient Centric Design in PFS Product Development**  
- *Justin M. Wright, PhD, Director, Pharmaceutical Development, BD*



- **Regulatory Considerations for Pre-Filled Syringes— Updates on the New and Proposed USP Chapters for Parenteral Drug Products**  
- *Presentations by Michael Eakins & Michael A. Ruberto, USP Expert Committee Members*



- **Glass Coated Plastic Pre-filled Syringes**  
- *Peter J. Sagona, Vice President, SiO2*

- **E&L Considerations for Drug-Filled Implantable Devices**  
- *James R. Scull, General Manager, NSF Health Sciences*



- **Method to Extract and Quantify Elemental Tungsten from Pre-Filled Syringes**  
- *Kiyoshi Fujimori, Senior Associate Scientist, Amgen*

- **Comparison of Product Behavior During Lyophilization When Processed in Dual Chamber Cartridges and Tubing Vials**  
- *Michael S. Thomas, Senior Research Scientist, Lyophilization Technology, Inc.*

## And Much More! Including Special Coverage On:

- \* Sterilization Solutions for Pre-Filled Syringes
- \* Aseptic Transfer of Pre-Filled Syringes

- \* Next Generation Materials & Design of Pre-Filled Syringes
- \* Extractables/Leachables Considerations for Pre-Filled Syringes

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**Monday, May 19, 2014**

8:00 Complimentary Breakfast & Chairperson's Welcome and Opening Remarks

## Strategic Development & Design Considerations

8:30 **Pre-Filled Syringe Manufacturing: A Review of Processes and Challenges**  
*Dr. Gregory A. Sacha, Senior Research Scientist, Baxter BioPharma Solutions*

The pre-filled syringe for parenteral administration of medications is a popular dosage form that offers advantages for the manufacturer as well as the patient and health care professional. The advantages have increased their use and have led to the development of new types of syringes and automated injection devices. The objective of this presentation is to introduce the delivery system and its uses, describe the manufacturing processes for the syringes, and describe the filling and sealing processes for the drug product. The discussion will include the challenges encountered during manufacturing and challenges that may be encountered during drug product development.

9:10 **Linking Technology with Patient Centric Design**  
*Justin M. Wright, PhD, Director, Pharmaceutical Development, BD*

Successful design of a drug delivery system requires careful consideration of patient needs and preferences for a given therapeutic area balanced against a drug product's chemical and physical characteristics which may contribute to the overall system performance. Patient-centric design is an iterative approach to product development which is intended to improve patient acceptance, adherence, and ultimately product preference. While this approach keeps the patient at the center of the development process it does require the availability and knowledge of the corresponding primary container technologies which permit the development of a system at the requisite performance level.

In this talk, we will describe the importance of patient centricity in product design and illustrate how this design methodology can be incorporated and managed with primary container product innovations. Additionally we will review the many dimensions required for successful product development and the interconnectivity of system attributes.

Examples to be discussed include needle innovations, strengthened glass, cross-linked silicone, and improved safety and injection devices.

9:50 *Mid-Morning Break and Exhibit Viewing*

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10:10 **From Formulation to Final Product**  
*Dr. Andreas Rothmund, Vetter Pharma*

Selecting the optimal container closure system for a new drug product is not an easy task. Selection is influenced by multiple aspects such as drug substance stability/formulation, dosing scheme, patient population but also availability of components, required fill/finish technology and even thoughts on life-cycle management aspects.

After introducing some of the interdependencies between those aspects, this talk will, using a set of simple questions, help you to find the container closure system that will suit your and your new drug's needs best.

10:50 **Glass Coated Plastic Pre-filled Syringes**  
*Peter J. Sagona, Vice President, SiO2*

The pre-filled syringes used today are made from either type 1 borosilicate glass or plastics such as cyclic olefin copolymer (COC) or cyclic olefin polymer (COP). Glass containers (syringes, vials and cartridges) are prone to breakage and particles, incorporate trace metal contaminants and have larger dimensional tolerances compared to plastic containers. Plastics mitigate some of the problems associated with borosilicate glass but plastics lack adequate barrier properties to environmental gases and solute molecules that can leach into the drug. Our glass coating system applies a thin layer of pure SiO<sub>x</sub> glass with a top protective layer and lubricity coating on plastic syringes. A 35–50nm thick SiO<sub>x</sub> coating provides barrier properties to oxygen and leachable impurities. A siloxane top layer over the SiO<sub>x</sub> layer makes the coating system compatible with higher pH drug formulations. We have shown that our coated plastic, pre-filled syringes are chemically and physically robust, have excellent barrier properties, have superior dimensional tolerances to glass, have low extractables and leachables and are friendly to sensitive proteins. Our novel lubricity coating is well adhered to the surface and delivers break loose and glide forces comparable to traditional silicone oil lubricants. A scalable manufacturing process for producing glass coated plastic pre-filled syringe has been developed and is operational.

11:30

## Developing an Innovative Approach to Scale Up of Transfer of Sterile Prefillable Syringes and Other Components into Production Barrier/ Isolator Filling Environments

*Howard Drake, Vice President, Ompi*

Loss of sterility a contamination risk is becoming more and more an issue under the lens of FDA inspectors as critical factors in the pharmaceutical manufacturing injectable process. Recently some concerns have arising relation to the efficacy of the common decontamination procedures (ebeam, VHP, Alcohol) applied on transfer material such us nest and tub configuration. This presentation aims to illustrate:

- the solutions and benefits of the EZ-fill™ range of sterile, ready to use glass containers for parenteral use;
- how to assure sterility reducing procedures and cutting costs related to validation, capex.

The packaging solution presented targets the supply chain of ready to use glass containers for the pharmaceutical industry. Its main objective is to transfer the washing and sterilization steps from the pharmaceutical companies to the glass primary package manufacturers. The pharmaceutical company is therefore left with the only filling and final capping phases. The strong innovation of the solution proposed is supported by the development of a new sterile bigbag packaging system (STERI BIGBAG), that will allow to maintain the container sterility from the producer site to the customer site; the STERI BIGBAG can be equipped with an all-plastic transfer port, with a new design, for the direct interface and transfer of the packaging to the sterile working areas, both with human and automated operators, thanks to newly developed plastic trays and nest/tubs that are able to grant the glass container cosmetic integrity and operability. The environmental benefits deriving from these implementations will imply a reduction in the consumption of electric energy and water; heavy machinery disposal and rejects will be reduced as well. Economic benefits will follow: in particular, the customer is expected to save the costs related to the plants, in particular to their maintenance, operating and disposal procedures.

- Loss of sterility a contamination risk is becoming more and more an issue under the lens of FDA inspectors as critical factors in the pharmaceutical manufacturing injectable process
- There is the need for a packaging solution able to assure sterility reducing procedures and cutting costs related to validation and capital investment.
- We illustrate the development of a new sterile bigbag packaging system (STERI BIGBAG), that will allow to maintain the container sterility from the producer site to the customer site

12:10

*Complimentary Lunch and Exhibit Viewing*

## Critical Issues - Regulatory Considerations for Parenteral Drug Products

1:30

### Proposed Changes to USP's General Chapters on Parenteral Packaging Components

*Michael Eakins, Eakins & Associates; Vice Chair, USP Expert Committee*

USP General Chapters are regularly revised with new chapters being added. The presentation will review changes to packaging material chapters on glass, plastic and elastomers and discuss the new General Information Chapters on extractables, leachables and the chapter covering the inner surface durability of glass containers. Chapters on analytical methods are also being updated. Changes in chapters covering elemental impurities, spectroscopy and particulate inspection will be discussed.

2:10

### A Discussion of the New USP Chapters Designed to Establish the Suitability for Use of Plastic Packaging for Pharmaceutical Products

*Michael A. Ruberto, Material Needs Consulting; USP Expert Committee*

It is essential to ensure that container closure systems (CCS) for the packaging and delivery of parenteral products do not adversely interact with the drugs to affect their safety or quality. Chemical entities from the packaging components, whether they are constructed from glass, metal, plastic, or rubber, can migrate or leach from these materials and into the drugs. For years, the established procedures for the safety evaluation of parenteral packaging systems involved antiquated compendia methods along with best practices established for inhalation products which used ultra conservative thresholds and extraction conditions used to mimic the solvating power of drug formulations that are often very different from parenteral products. Recently the United States Pharmacopeia (USP) has published draft general chapters that recommend a three stage approach to establish the suitability for use of packaging materials using a combination of enforceable and informational general chapters. This approach includes a major modernization of USP <661> now entitled "Plastic Packaging Systems and Their Materials of Construction" along with the publication of two new chapters, USP <1663> "Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems" and <1664>

“Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems”.

This presentation will provide:

- A summary of these newly issued documents
- Define the specific requirements and recommended methodologies for extractables and leachables testing for parenterals
- Discuss roles and responsibilities for vendors and pharmaceutical companies

2:50 *Afternoon Coffee Break and Exhibit Viewing*

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## ZEON

3:10 **The Effect of Various Sterilization Modes and of Syringe Storage Conditions on the Gliding Behavior of Uncoated and of Fluoropolymer-Coated Pre-Filled Syringe Plungers**

*Renaud Janssen, PhD, Datwyler Packaging*

Prior to aseptic filling prefilled syringe plungers can be sterilized in various ways. Steam sterilization followed by drying and sterilization by gamma irradiation are the two most frequently encountered sterilization modes. The results of a study on the effect of sterilization on the gliding behavior of uncoated syringe plungers and of fluoropolymer-coated plungers in the same rubber formulation will be presented. Discrimination will be made between breakloose and gliding forces. The fact that prefilled syringes before use may be stored at different temperatures has been taken into account into the study.

Fluoropolymer-coated plungers are used in applications where the contact of the drug formulation with the uncoated rubber is critical in terms of compatibility or where the silicone that is applied in the last manufacturing step of such closures leads to complications. (Note: results will be presented in an ‘anonymous’ form with respect to the trade names of the products, thus avoiding confusion with commercial promotion).

Take home benefits

- Learn about the effect of steam sterilization and of gamma irradiation on breakloose and gliding forces in prefilled syringes
- Collect information on the impact of syringe storage temperature on gliding behavior
- Results for uncoated and fluoropolymer coated plungers are presented next to each other.

3:50 **Aseptic Transfer of Pre-Sterilized Syringes**  
*Jamie Schroetter, Business Development Manager, Robert Bosch Packaging Technology*

- This presentation will cover the techniques used for handling nested pre-filled syringes. Topics examined include:
- Nested syringe handling techniques
- Nested syringe transfer into sterile filling core
- Technology options for the filling and closing of nested syringes

4:30 *End of Day One*

## Tuesday, May 20, 2014

8:00 *Complimentary Breakfast & Chairperson’s Remarks*

### **Critical Issues - Elemental Impurities**

8:30 **Method to Extract and Quantify Elemental Tungsten from Pre-Filled Syringes**  
*Kiyoshi Fujimori, Senior Associate Scientist, Amgen*

Elemental tungsten is a known leachable from PFS with detrimental effects on certain filled drug products. To ensure quality and minimize risk, a unique method was developed to efficiently extract tungsten from PFS and quantify accurately/precisely the extracted tungsten by ICP/MS. Various extraction conditions and quantification factors/techniques were considered and compared for.

- Understand the importance of monitoring tungsten levels in PFS to ensure product quality.
- Presentation of method to extract and quantify tungsten from PFS.
- Compare factors/techniques that affect tungsten extraction efficiency.
- Determine ICPMS conditions that allow for accurate and precise tungsten quantification.

### **Spotlight on Product Behavior in Dual Chamber and Tubing Vial Dosage Forms**

9:15 **Comparison of Product Behavior During Lyophilization When Processed in Dual Chamber Cartridges and Tubing Vials**  
*Michael S. Thomas, Senior Research Scientist, Lyophilization Technology, Inc.*

Product behavior during lyophilization for material processed in a dual chamber cartridge can be considerably different from the same material processed in a vial. This often warrants unique assignment of the critical independent variables of shelf temperature and cham-

ber pressure to process with success. Evaluated in this study was the influence of the novel container/closure system of a cartridge compared to the more traditional vial and stopper combination. A Mannitol solution was filled onto a full tray of both 1 cc cartridges and 3 cc vials and processed simultaneously. The thermal profiles of multiple product containers of each type were assessed during each phase of the lyophilization cycle (loading, freezing, primary and secondary drying). Finished product was evaluated to compare the impact of varied product response during processing. The results demonstrate the importance of understanding product behavior during manufacture of lyophilized drug into these two unique dosage forms.

11:50

*Complimentary Lunch and Exhibit Viewing*

## **Best Practices for Sterilization**

1:20

### **Sterilization Solution for Prefilled Syringes** *Dr. David Opie, PhD, Senior Vice President, Research and Development, Noxilizer, Inc.*

Prefilled syringes are rapidly becoming the most preferred delivery devices for various categories of injectable drugs. According to a November 2013 report, *Prefilled Syringes Market (Glass and Plastic) - Global Industry Analysis, Size, Volume, Share, Growth, Trends and Forecast, 2013 - 2019* by Transparency Market Research, there are over 60 types of drug prefilled syringes available in the market with many more in product pipelines. Further, boosted by increased use of biologics and injectable drugs, technical advances in manufacturing and packaging, and rising demand for self-administration, this report predicts the global market for prefilled syringes will reach 4.98 billion globally by 2019 with the North American market growing at a 15% CAGR.

This explosive growth is not without challenges for drug developers and manufacturers. Among the challenges, developing best manufacturing and sterilization practices (within the limitations of glass and polymer systems), managing safety and navigating regulatory concerns. Further, for those prefilled products administered in a sterile field that require surface sterilization—the limitations of traditional sterilization processes (EO, gamma, steam and hydrogen peroxide) pose greater challenges.

Nitrogen dioxide (NO<sub>2</sub>) sterilization is gaining recognition as a highly-effective and economical, room temperature sterilization alternative ideally suited for prefilled syringes. It eliminates preconditioning, reduces aeration time and maintains material properties in heat-sensitive products. And recent research has revealed NO<sub>2</sub> can surface sterilize and depyrogenate polymer syringes at room temperature and ambient pressure in a short cycle time (less than 2 hours) without diffusing past the stopper. This new alternative will be discussed in the context of a case study, detailing mechanism of kill, cycle parameters, residuals, biocompatibility, safety and economic benefits.

Session participants will benefit from:

- Continued education on current and emerging sterilization technologies for prefilled syringes
- Clearer understanding of the benefits and limitations of available technologies
- Detailed case study on prefilled syringe sterilization with nitrogen dioxide (NO<sub>2</sub>) gas
- Focused solution that directly addresses safety concerns for prefilled syringe drug manufacturers

10:00

*Mid-Morning Break and Exhibit Viewing*

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## **Extractables & Leachables Considerations**

10:20

### **E&L Considerations for Drug-Filled Implantable Devices** *James R. Scull, General Manager, NSF Health Sciences*

Drug-Filled implantable devices represent a unique challenge when it comes to evaluating extractables and leachables. As opposed to simple drug-coated implantables, in which both drug and device compounds leach into the body, drug-filled implantables serve as a drug reservoir where the drug elutes through the device rather than off of it. In developing an extractables and leachables testing program for drug-filled implantables, three primary actions must be considered; 1) leaching of device related compounds into the body, 2) leaching of device related compounds into the drug reservoir and 3) leaching of drug-device compound adducts into the body. In addition, leachables from the device into the drug reservoir may negatively impact the safety and/or efficacy of the drug itself.

In general, the study should incorporate components of ISO 10993, PQRI and USP as well as a simulated-use assessment. Considerations for an extractable and leachable study design, execution and data interpretation will be presented along with a specific case study for an ophthalmic drug-filled implantable device.

11:05

### **Extractables/Leachables in Pre-Filled Syringes** *John Iannone, Program Manager, Toxikon*

Abstract Coming Soon.

2:05

## Strategies for Elastomer Components Intended to Minimize Patient Risks

**Tibor Hlobik, Global Director, Marketing for PFS Technologies, West Pharmaceutical Services**

During Drug product development and lifecycle management with pre-filled syringes, companies are facing risks in areas of extractables and leachables, material defects, particles including sub-visible and visible, and functional performance. It is essential that components, especially plungers used to package and deliver drug products, be of the highest quality and properly selected to meet complex user requirements. In this talk, we review component selection criteria, new plunger technology for increased levels of drug protection, and how major biotech and pharmaceutical companies are meeting increasing quality, regulator and patient requirements.

2:50

*Afternoon Coffee Break & Exhibit Viewing*

3:10

## Technical Data Update – Cyclo Olefin Polymer (COP)

**Toshiro Katayama, Product Manager – New Business Development, Zeon Chemicals**

Cyclic Olefin Polymer (COP) is very pure, amorphous, high transparent and non polar plastic with excellent chemical resistance and moisture barrier. COP can be extruded, injection molded and blow molded and they are EtO, Gamma and steam sterilizable. This presentation will cover:

- Key properties and features of COP & its benefits for Pre-filled syringe applications

- Introduction of new grade, ZEONEX 5000 - low Tg, high Elongation & high moisture barrier grade
- Mechanical properties after exposure to gamma, steam, EOG and cryogenic temp
- JP, US, EU Pharmacopoeia and ISO 10993 status
- Moisture/Gas barrier data
- Residual metal and outgas data
- COP marginal stress data vs. various chemicals
- Protein Adsorption study with BSA, Insulin, IgG
- EB & Gamma irradiation -color shift study
- Comparative mechanical properties of COP vs. Glass & COC

3:55

## Case Study: Pre-filled Syringe Inspection for Viscous and Non-Viscous Products

**Michael Kerbaugh, Sales Application Engineer, Bosch Inspection Technologies**

*This case study presentation will detail the technologies applied for particulate and cosmetic inspection of products with varying viscosities. Technologies to be presented include: Direct Spin System, SDx Static Division, Camera Vision for Slow-moving (Image Subtraction), Heavy and Floating Particles; and contact free glass-to-glass syringe handling. Also, a review of the defect kits used for machine design, validation and daily challenge.*

- Nested syringe handling techniques
- Nested syringe transfer into sterile filling core
- Technology options for the filling and closing of nested syringes

4:30

*Close of Program*

# 7<sup>th</sup> Annual Pre-Filled Syringes Forum

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 Venue: **The Racquet Club of Philadelphia**  
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