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Pre-Filled Syringes Forum 2013

Strategic Development, Inspection, Safety & Regulatory Compliance and Commercialization of Pre-Filled Syringes

JUNE 6-7, 2013, RACQUET CLUB OF PHILADELPHIA, PHILADELPHIA, PA

Featuring Case Studies and Lessons Learned from Industry Experts!

- MATERIALS, DESIGN & CONSTRUCTION OF PRE-FILLED SYRINGES
- SAFETY CONSIDERATIONS & REQUIREMENTS
- NUMEROUS DEVELOPMENT CASE STUDIES
- MANUFACTURING & FILLING SOLUTIONS
- REGULATION & INSPECTION OF PRE-FILLED SYRINGES
- FUTURE MATERIALS FOR PRE-FILLED SYRINGE COMPONENTS

Including Special Coverage On:

- Syringe Plunger Movement
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- Container Closures
- Stopper Movements
- Elastomeric Components
- Syringe Manufacturing
- Extractables & Leachables
- Combination Products

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Thursday, June 6, 2013

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

FDA QUALITY SYSTEMS UPDATE

9:00

Explore the Current State of FDA Quality System Requirements for Drug Delivery Systems

Michael Gross, Ph.D., RAC, Principal Consultant, Chimera Consulting North America LLC

This presentation will analyze and discuss the FDA's recently published final rule, Current Good Manufacturing Practice Requirements for Combination Products. It will focus on key elements of the new regulation and what pharmaceutical and medical device companies must do to comply with its requirements. The discussion will consider the fact that FDA definitively declared in the preamble to the new regulation that prefilled syringes and kits are combination products and therefore their development and manufacture must be conducted in compliance with both drug/biologic CGMP and device QSR requirements. How and when to apply Device Design Controls in the development and manufacture of drug delivery systems will also be considered.

9:45

Pharmacopeial Control of PrimaryPrimary Parenteral Packaging Components

Michael Eakins, President, Eakins and Associates, Inc.

"The United States Pharmacopeia (USP) contains general chapters covering elastomeric, glass and plastic primary packaging components. Revisions to <660> Containers-Glass and a new chapter <1660> Evaluation of the Inner Surface Durability of Glass Containers will be described. Two new draft guidance chapters covering the principles of extractables and leachables are in preparation in conjunction with the revision of <661> Containers-Plastics. In addition, the chapter describing the test for Heavy Metals (<231>) will be deleted in 2014 and replaced by 2 new chapters <232> Elemental Impurities—Limits and <233> Elemental Impurities—Procedures and the new method will be a part of the proposed revision of <661>. Guidance on microbiological methods to evaluate the integrity of sterile product packaging are already present in the USP. A draft chapter has been prepared in order to add guidance on physico-chemical methods for integrity evaluation of sterile product packaging to the USP. The presentation will review the chapter revisions and the new proposed chapters as they relate to containers for parenteral packaging in general including pre-filled syringes."

10:30 *Mid-Morning Break and Exhibit Viewing*

MANUFACTURING APPROACHES

10:45

Anticipating Developments on Primary Containers: A Manufacturing Practical Approach

Howard Drake, Vice-President, Ompi of America

High-end biotech products continue to enter the market posing new technical challenges the development of injection systems. Primary packaging for parenteral is exploring new materials and new technologies around all the typical themes involved with these systems: mechanical resistance, surface quality, gliding performances, optional formats, etc. In these development pre-filled syringes are playing an increasing role thanks to their superior performances of an injection system, as a replacement of the legacy reconstitution procedures for vials. New manufacturing process and advanced technology have been developed and now available is a new range of primary packaging in ready to use formats that can successfully shift the pfs-paradigm.

- Requirements from pharma and regulatory
- Identification of criticalities
- Feasibility study based on a DOE
- Going from the need to a prototype
- A new concept

11:30

Pre-filled Syringe Processing with RABS, Isolators, E-beam & Alternatives

Jim Spolyar, Sales and Technical Director, SKAN US, INC

This presentation will highlight the aseptic processing lines that have been installed for pharmaceutical syringe filling around the world. There will be an analysis of RABS and Isolator technology, as well as the use of E-Beam for tub entry, with some alternatives for low speed production. Also the latest isolator for aseptic/toxic nested syringe filling. Also, a short presentation on total clean room de-contamination with H2O2 vapors

- Isolator technology with latest E-Beam design features
- Alternative tub entry system for slow speed production
- Expansion of the areas of nested syringe filling technology to aseptic/toxic
- Comparison of use of RABS to Isolators
- Total cleanroom decontamination using H2O2 vapors

12:15 *Lunch & Exhibit Viewing*

TESTING & INSPECTION SOLUTIONS

1:30

Facilitating Extractables and Leachables Testing Using a Preliminary Materials Assessment

Michael A. Ruberto Material Needs Consulting, LLC

The characterization and control of extractables and leachables from the plastic and elastomers used in prefilled syringes is a formidable task for the pharmaceuti-

cal industry. These materials often contain stabilizers, colorants, fillers, and other specialty additives, making their formulation much more complex than metal or glass, and therefore, a greater risk for leachables. Performing a comprehensive materials assessment prior to conducting an extractables or leachables study can be a useful tool to predict migrants, design a suitable controlled extraction study, facilitate data analysis, verify vendor supplied materials information, and evaluate supply chain integrity. This presentation will utilize a combination of chemistry and case studies to demonstrate the attributes of a materials assessment based on a thorough understanding of the polymers and additives used to fabricate pre-filled syringes. Topics discussed in this presentation will include:

- Polymer and additive chemistry
- Factors that affect migration from polymers
- Typical extractables profiles for the materials used in pre-filled syringes
- Case studies to demonstrate the application of a materials assessment for risk management

2:15 **Innovative Glass Plasma Coated Prefilled Syringes**

Dr. Kevin Turney, Si02 Medical Pruducts

Current commercially available pre-filled syringes are made from borosilicate glass or plastics such as cyclic olefin copolymer (COC) and cyclic olefin polymer (COP). Glass containers are prone to breakage, cracking, delamination, trace metal contaminants and poor dimensional tolerances. COC and COP mitigate many of the problems associated with borosilicate glass but they lack adequate barrier properties to oxygen and solute molecules. An innovative new plasma glass coating system applies a thin layer of pure SiOx glass with a top protective coating on plastic syringes. A 35 – 50 nm thick SiOx coating provides barrier properties to oxygen and impurities. A highly-crosslinked siloxane-based product contact coating, approx. 200 nm thick, over the SiOx coating provides protection from hydrolytic digestion of the SiOx glass. Various methods, including plasma deposition of additional siloxane-based layers, to produce a lubricous surface resulting in superior and uniform break loose and glide forces will be presented. Pre-filled syringes made from plastic and coated by this innovative process are chemically and physically robust, do not delaminate, are not prone to breakage, have excellent barrier properties, superior dimensional tolerances to glass, low extractables and leachables and are protein compatible. The new syringes offer all the advantages of plastic and glass without any of the weaknesses of either.

3:00 *Afternoon Break*

3:15 **Non Destructive Automated Method for Pre-Filled Syringes Closure Integrity Testing compared with Dye Ingress Testing**

Scott Heins & James Kearbey, Bonfiglioli Engineering North America.

One of key aspects of Pre-Filled Syringes (PFS) quality control is the assurance of closure integrity after filling and terminal sterilisation. Leaking through the PFS is a crucial defect which exposes the drug to the risk of contamination. First the presentation describes a Container Closure Integrity Testing (CCIT) technology applicable to PFS containers filled in with medicinal products. Innovative technical solutions are then detailed; controls to be used while managing the CCIT process so to consistently ensure the required level of quality, stability and repeatability are outlined as well.

Data and findings of a challenge test performed as stated in ASTM F2338-09 Standard Test Method for Nondestructive Detection of Leaks in Packages by Vacuum Decay Method are provided. The study demonstrates that a Bonfiglioli Engineering S.p.A. Vacuum Decay CCIT equipment is effective and reliable in detecting leakages ≤ 5.0 µm in PFS. The achieved results are compared with destructive methylene blue dye ingress method as referred in world Pharmacopoeias. A suitable set of defective PFS with 5 µm, 10 µm, and 20 µm laser-drilled holes below and above fill level, have been employed to determine both the detection time and test efficiency/repeatability.

4:00 **Polymer Syringe and Cartridge System For Delivery of Biologics**

Scott Young, Strategic Market and Technical Development, Daikyo Crystal Zenith, West Pharmaceutical Services, Inc.

Formulation of the newer biologics at high drug concentration places unique demands on packaging and delivery systems. In addition to an increased propensity to aggregate, protein solutions at high concentration frequently have higher viscosities which can create issues in drug administration. Recent regulatory scrutiny of glass particles and delamination has also added to the challenges to drug delivery combinations. These market factors have generated renewed interest in plastic delivery systems. This discussion will focus on Daikyo Crystal Zenith (CZ) plastic prefillable syringe systems and cartridge based on-body injectors for large volume delivery. Attributes such as break resistance and the absence of silicone, tungsten and adhesives as they relate to storage systems for biopharmaceuticals will be discussed with appropriate case studies. The discussion will also review the use of sterile CZ vials that are effective for cold temperature storage of biopharmaceutical and cell therapy products.

4:45 **New Sterilization Solution for Pre-Filled Syringes**

Dr. David Opie, Ph.D, Sr. Vice President, Research and Development, Noxilizer, Inc.

The number of biotech drugs being delivered via pre-filled syringe is growing at a rapid pace. According to a March 2013 report from Daedel Research, Global Pre-Filled Syringes Market: Trends & Opportunities (2012-2017) pre-filled syringes have become the preferred drug delivery device for over 50 injectable medicines and vaccines. Additionally, pre-filled syringes accounted for $2.9 billion of the $11.36 billion global injectable market in 2011, and are expected to cross $6 billion in the year 2017. An increasing number of these products are administered in the sterile field and are required to be sterilized on the surface too. This is a challenge given the traditional sterilization processes (EO, gamma, steam and hydrogen peroxide). There is now a nitrogen dioxide (NO2) gas sterilization process that is room temperature, leaves no cytotoxic residuals, operates without a vacuum, provides surface sterilization and maintains material and drug integrity. This new alternative will be discussed using a case study, including: mechanism of kill, cycle description, residuals, data that demonstrates biocompatibility, limitations, and the safety and financial benefits of bringing sterilization in house.

This session will provide the following benefits:

- **Continued education on current and new sterilization processes;**
- **Understanding of the benefits and limitations of nitrogen dioxide sterilization; and**
- **Allow attendees to become a resource to their organization on the challenges and solutions of sterilizing pre-filled syringes.**

5:30 ***End of Day One***

Friday, June 7. 2013

8:30 ***Breakfast & Chairperson's Opening Remarks***

9:00 **Recent Developments in Prefilled Syringes**

Pattty Kiang, PhD, Kiang Consulting Services

The advantages for drug developers using pre-filled syringes are numerous; improved patient compliance and better cost efficiency, as well as mitigating the risks of drug wastage and product contamination. However, this rapidly expanding area is not without its hurdles.

Prefilled syringes act as the primary container for drug products. Therefore, they are required to provide seal integrity, compatibility and drug stability through the shelf life of the drug product.

There are some challenges associated with the current staked needle glass syringe system: the potential organic and inorganic chemical compounds have a tendency to leach into the drug solutions. Surface silicone oil has caused protein drug aggregation and residual tungsten from the staked needle insertion process has caused protein degradation. Glass breakage problems have been the reason for several glass prefilled syringe product recalls.

Without switching to plastic prefilled syringes, incremental improvements have been made, such as the optimized siliconization process, better controlled needle insertion process and better packaging design and handling systems.

Besides the process improvement, there are new needle safety devices that have been developed, some retractable needle designs have been introduced into market, and it takes less space and generates less waste.

9:45 **Integrating Quality by Design for Development of Prefillable Syringe Components**

Jason Mattia, Program Manager, R&D – PFS, West Pharmaceutical Services

Product, process and control understanding based on sound science and risk management are a "Must" not a "Nice-to-Have" for primary packaging components used for prefilled syringes. Elastomeric closures in combination with the primary container are a critical element of the total drug product as delivered to patients and it makes sense that these components are developed using Quality by Design requirements to minimize risk.

This presentation will provide details into how significant advances in quality can be achieved using patient needs as part of a development strategy for new components, executing development based on a systematic approach, and driving continuous improvement of the industrialized product based on a body of knowledge.

Specifics of the presentation to include:

- **Trends that are driving new elastomeric component technology**
- **Case study of a new component development from Concept through Industrialization.**
  - **o How to identify Patient and Pharma needs**
  - **o "Critical Quality Attributes" used to drive design and process**
  - **o Defining and executing on design variables**
  - **o Modeling with "Finite Element Analysis" and proving with experimental tools**
  - **o Statistical data drives product decisions**
- **How product knowledge can minimize "Surprises" and improve "Trust"**

10:30 ***Mid-morning Break and Exhibit Viewing***

10:45 **Testing and Validation Aspects of Pre-Fillled Syringes**

John Klostermyer, VHP Applications Developer, STERIS Corp

VHP is gaining acceptance for the terminal sterilization of heat sensitive products packaged in Tyvek trays. This presentation addresses when the use of VHP may be appropriate and, depending on the characteristics of the

product, which type of VHP system is best suited. Early stage testing, scaling up and aspects of validation will also be covered. Different products and applications will be presented.

This presentation will provide insight about:

- When it makes sense to use VHP
- What types of products are being sterilized with VHP
- Types of systems
- Process challenges and limitations
- Minimizing risk in process development
- Examples – products and chambers

11:30 **One Step Closer to Zero Defect Manufacturing of Pharmaceutical Rubber Closures**

Renaud Janssen,Global Director of Scientific Affairs,R&D and Technology Department, Datwyler Pharma Packaging

This presentation describes the innovative approach that Datwyler Pharma Packaging adopted in the design and operation of its FirstLine plant in Alken, Belgium. Market requirements for rubber closures in the areas of absence of biological contamination and of cosmetic imperfections over the years always have been increasing. As the first of all manufacturers of pharmaceutical rubber closures Datwyler translated these market challenges into a new concept of closure manufacturing. The presentation gives an overview of all of the preventive measures that were taken to avoid defects to the highest possible extent, as well as of the corrective measures that were implemented to eliminate residual defects.

- The elastomeric closure manufacturing process
- Responding to increasing market requirements
- Preventive measures for improvement
- Corrective measures for improvemen

12:15 *Lunch*

1:45 **Exploring Future Materials for Pre-Filled Syringes**

Toshiro Katayama, Product Manager, Zeon Chemicals L.P.

Use of clean, inert and transparent plastics continue to grow in pre-filled package applications as breakage and contamination concerns over glass containers increase. ZEONEX Cyclo Olefin Polymer (COP) has been the plastic of choice for pre-filled package and use of COP based containers are expected to grow at fast rate in next few years.

The presentation will cover:

1) Key properties of COP and its Regulatory Status and Bio-Compatibility, Protein Adsorption data, effect of Gamma/EB/Steam sterilization/Aging data (Mchanical & Optical) after sterilization
2) Introduction of new products and technologies

INSPECTION SOLUTIONS

2:30 **Final Quality Approach using X-Ray Based Particle Detection, Vacuum Based Integrity Testing and Visual Inspection**

Patrick Schlatter, WILCO AG

This session will explore the latest inspection technologies under one machine platform providing a Quality Declaration on pharmaceutical products.

This FINAL QUALITY approach combines CCI testing, headspace analysis, foreign particle detection, cosmetic inspection or any combination thereof at production speeds of 600cpm and more, resulting in major cost and footprint savings.

3:15 **Parylene: High Performance Surface Modifier for Pre-filled Syringes**

Juan Gudino, Manager, SCS Coatings

Parylene polymeric surface modifications have been used in the pharmaceutical and medical device industries for well over thirty years. New applications continue to arise whenever it is necessary to prevent or control moisture, fluid or chemical penetration, prevent trace element leaching or extraction from devices and pharma contents or containers or simply to make a surface biocompatible. This presentation addresses Parylene's utility in solving such issues and reviews applications where the polymer has been used to protect components and devices from otherwise undesirable degradation, damage or contamination.

Parylene coatings have been utilized in the medical and pharmaceutical industries for numerous reasons:

- To provide or enhance the bio-acceptability of the device being coated.
- To provide chemical and moisture barrier protection to any substrate preventing extractables /leachables.
- To improve the lubricity (preventing stiction) of parts and products.

4:00 **Automatic Syringe Inspection – Design for High Performance**

John McEwen, Bosch Inspection Technology Inc.

Many factors contribute to the performance success of an automated syringe inspection project. This presentation will cover the machine design characteristics required to achieve high detection and production performance with minimal false rejects and long life cycle. Topics to include: SD Particle Inspection, Cognex Vision Systems, Hybrid Inspection, Oscillating Drive Mechanism, Non-Vacuum Sorting System and Re-Inspection Strategies. Additionally, a review of defect kit type and quantity needed for machine validation and design for eliminating glass-to-glass contact for improved product quality.

4:45 **Development of Concentrated Suspensions in Prefilled Syringe Container Closure Configurations**

Jen Vandiver,Scientist III, Alkermes

Long-acting injectable (LAI) drug products have an important and growing role in treating chronic diseases. LAI's can be formulated to take advantage of the inherent physico-chemical properties of low solubility compounds by enabling the crystalline materials to form a depot in tissue from which the active pharmaceutical compound (API) is delivered by slow dissolution and/ or diffusion for a period of weeks to months. Development of concentrated aqueous suspensions of LAIs in prefilled syringe (PFS) container closure systems offer an opportunity for drug delivery from an elegant and convenient presentation. In this work, we report on several aspects of PFS development including:

- **Selection of primary components and assessment of compatibility and functionality.**
- **Impact of headspace on drug product performance, manufacturing, and shipping.**
- **Complexity of developing drug/device combination products.**

5:30 ***Close of Conference***

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