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PharmaED's

Pre-Filled Syringes Forum 2011

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

MARCH 10-11, 2011, CROWNE PLAZA DOWNTOWN, 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
- Development Case Studies
- Manufacturing Solutions
- Visual Inspection
- Container Closures
- Stopper Movements
- Elastomeric Components
- Syringe Manufacturing
- Extractables & Leachables
- Combination Products

Featuring Representation From:

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Biologics Consulting Group
Kiang Consultant Services
West Pharmaceutical Services, Inc.
Vetter Pharma-Fertigung GmbH
Schott North America, Inc.
Trotter Biotech Solutions
Schreiner MediPharm, LP
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Thursday, March 10, 2010

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

MATERIALS, DESIGN & CONSTRUCTION

8:45 **Future Materials for Pre-filled Syringe Components**
Dr. Patty Kiang, President, Kiang Consultant Services

Pre-filled syringes are becoming a popular tool for sterile injectable drugs due to its ease of use, enhancements in compliance, and reduction of waste of expensive drugs and marketing differentiation. There are still some drawbacks due to the breakage of glass barrels, silicone oil coatings on the inside of glass barrels causing protein aggregation, Tungsten vapors causing Protein degradation, rubber plunger leachables causing toxic effects, etc. Due to all these reasons there is a definite need for better syringe construction material and components. A special clear plastic pre-filled Syringe with Flurotec laminated rubber plunger, without silicone oil lubricant and Tungsten to eliminate leachable and protein aggregation concerns will be discussed.

9:30 **Managing the Impact of a Material Change in Components of Pre-Filled Syringes**
Dr. Michael A. Ruberto, President, Material Needs Consulting, LLC

The characterization and control of extractables and leachables from the plastic and elastomers used in pre-filled syringes is a formidable task for the pharmaceutical industry. Obtaining information from vendors regarding the composition of container closure system components can be a challenge, and even when this data is initially supplied, the communication of material changes that can affect the leachables profile of these components during development or after commercialization can be an issue. The supply chain associated with the fabrication of pre-filled syringe components can be quite complex. There are many suppliers of raw materials, such as additives and resins, that are further upstream and not under the direct influence of their downstream pharmaceutical customers. This presentation will provide a comprehensive review of the polymer supply chain for pre-filled syringe components as well as potential areas of concern. Case studies that illustrate the types of changes that can occur, both announced and unexpected, and their chemical and regulatory impact will be discussed. Specific topics will include:

- Introduction to polymers and additives
- Common changes to pre-filled syringe components
- Efficiently dealing with unexpected changes
- Implementation of control measures to evaluate new batches of components
- Partnering with vendors to establish an effective change control process

10:15 **Q&A**

10:30 *Refreshment Break*

10:45 **Exploring Future Materials for Pre-filled Syringes**
Toshiro Katayama, Product Manager, New Business Development, Zeon Chemicals L.P.

Cyclo Olefin Polymer (COP) allows for advanced, break-resistant packaging for protein-based, peptide-based, bio-pharmaceuticals and high-viscosity drugs, as well as contrast media. The presentation covers key basic properties of COPs, a color shift study after gamma and EB radiation, multi-layer package study with other plastics, chemical resistance data, Protein adsorption study, impact strength at cryogenic temp, and comparison of COPs with cyclic olefin copolymers.

ELASTOMERIC COMPONENTS

11:30 **Materials, Processes, Products and Quality of Pre-Filled Syringes**
Dr. Arno Fries, Director Product Management Tubular Glass, Gerresheimer

The pre-filled syringe industry is a dynamic sector serving pharmaceutical and biotech customers. In this presentation a speaker from the industry summarizes some of the factors shaping the market in the coming years:

- New syringe materials
- Add-ons for product life cycle management
- Advanced syringe manufacturing processes
- Syringe applications for biotech products
- Quality requirements

12:15 *Q&A*

12:30 *Pre-lunch Exhibitor viewing*

12:45 *Lunch* *Lunch Sponsor:* MG AMERICA A partnership for success

1:45 **Packaging Systems for Parenteral Administration of Biopharmaceuticals**
Dr. Vinod D. Vilivalam, Director of Strategic Market and Technical Development Daikyo Crystal Zenith, West Pharmaceutical Services, Inc.

The number of drug products packaged in injection devices is increasing, especially in the area of biopharmaceutical drug delivery. Newer proteins are characterized by higher doses, higher viscosities and are extremely sensitive to packaging materials. As a result, optimization of drug product stability in an injection device becomes critical in early stages of drug development process. The discussion will focus on a plastic pre-fillable syringe system that address various scientific and technological benefits . The presentation will include attributes of the Daikyo Crystal Zenith (CZ) 1 ml long pre-fillable syringe, that is break resistant, silicone oil free, and tungsten free, as it relates to drug storage systems for biopharmaceuticals, and that lends itself to a consistent performing delivery system when combined with an auto-injector. The discussion will also include sterile CZ vials and bulk container systems that are proven to be effective for low temperature storage for biopharmaceutical and cell therapy products.

2:30 **Fluoropolymer Coated Plungers for Pre-filled Syringes Technical Performance**
Dr. Renaud Janssen, Global Director of Scientific Affairs, Helvoet Pharma

This presentation explains why coated plungers are needed for a number of pre-filled syringe applications. The types of coated plungers that are offered to the market are discussed. Details are given on the performance characteristics of fluoropolymer coated plungers. The extractables & leachables characteristics of non-coated and of coated plungers are compared. Gliding behavior and container/closure seal integrity properties of coated plungers are illustrated for different types of barrels and barrel siliconization. Attention is equally spent to the Ready-To-Use format in which such plungers are available. Finally an update will be given to the audience on recent standardization efforts in the field of elastomeric pre-filled syringe components.

- Why are coated plungers for pre-filled syringes needed?
- Learn about performance characteristics of fluoropolymer coated plungers
- Get acquainted with the Ready-To-Use format for coated and for non-coated plungers
- Get an update on standardization efforts in the field of elastomeric pre-filled syringe components

3:15 **Q&A**

3:30 *Refreshment break*

DEVELOPMENT CASE STUDIES

3:45 **Polymeric Devices – Extractables and Leachables**
Mark Trotter, President, Trotter Biotech Solutions

Polymeric devices, disposable components, container/closure systems used as critical components of downstream processing and drug delivery should be carefully studied for polymer extractables and leachables which can influence the product quality. The presentation describes the various analytical techniques, such as RP-HPLC, GC-MS, FTIR and other testing to separate, identify, and quantitate polymeric extractables and leachables. Using such study methods as Modeling, Profiling and actual testing of product formulations will be explained and detailed. A review of recent PDA Extractables Interest Group and industry (BPSA) findings along with the current regulatory guidance (FDA / EMEA /ICH) standards and trends are discussed.

- Definitions of polymeric extractables and leachables in Pharmaceutical Processes.
- How to determine the requirements for qualification and quantification of extractables.
- What are the current industry and regulatory expectations and trends for extractable analysis?
- Review of the differing extractable methodologies; modeling, profiling and actual product testing.
- Where and when in the manufacturing process should extractables and leachables be of concern and how does the process parameters and formulation characteristics affect dosage, toxicity, surface areas, time, temperature, solvent systems.
- Ablity to identify applications where leachables testing vs. modeling is acceptable.
- Understand the concepts of extractables & leachables testing and modeling to assist in writing change control documentation and to meet regulatory requirements.
- Review various analytical techniques to separate, determine, quantitate and / or qualify using analytical instrumentation; HPLC, GC-MS, and FTIR.
- Determine which processes and polymeric products would need study and testing.
- 'How to' make determination which methodology, e.g., modeling, profiling and actual testing, is appropriate for the application

4:45 **Silicone deposition optimization in glass pre-filled syringes and real-time control of distribution and droplet size**
Howard Drake, Vice-President Ompi of America

Siliconization is an important step in pre-filled glass syringe production. The correct deposition profile is vital for ensuring the proper operation of autoinjector devices. Silicone oil is suspected of triggering the aggregation of protein and generation of sub-visibile particles if present in excessive quantity.
In the last year great efforts have been dedicated to techniques for controlling the deposition of silicone oil, droplet size and layer thickness designing special nozzles and characterizing the aerosol spray by digital imaging. The role of glass surface conditioning has been studied through the silicone oil contact angle measurement in different operating conditions and from several glass suppliers.
A step forward in the siliconization process will be to control 100% the deposited layer in production. The study investigated the different techniques available for measuring the silicone layer identifying the most suited for in- line integration. The development of an inspection unit capable of 12.000 syringes/hour is in progress .

5:15 **Q&A**

5:30 *Close of Day One*

Friday, March 11, 2010

8:30 *Chairperson's Day Two Opening Remarks*

8:45 **Quality Assurance of Syringe Components**
Dr. Andreas Rothmund, Vetter Pharma-Fertigung GmbH

This presentation will begin with an overview of syringe components and selection criteria. I will take you on a 'guided tour' through the quality aspects of syringe components.

Attendees will hear about critical quality attributes, types of defects and their origins. Gain insight into defect evaluation lists and will see the different contents of certificates.
The closing section will be focusing on aspects of supplier relationship and potential resulting consequences with regards to incoming testing.

QUALITY & REGULATORY CASE STUDIES

9:30 **Evaluation of Stability and Leachables Profile of Drug Products Dispensed Using Various Syringe Infusion Pump Configurations**
Kurt Moyer, Pharmalytica Services, Bristol, CT
The effect upon the stability of and leachables into representative drug products dispensed from 28 different syringes ranging in size from 1 to 60 mL by an infusion pump was evaluated. The drug products selected were Floxuridine for Injection, Dopamine for Injection and Morphine Sulfate for Injection. The syringes were filled separately with each drug product and loaded onto the infusion pump to be dispensed at a clinically relevant rate. Samples of the drug product were collected before entering the syringe (control sample) and after a predefined time at the set rate. These samples were then assayed by HPLC-UV and analyzed for volatile leachables by GC-MS, non-volatile leachables by LC-MS and inorganic leachables by ICP-MS. The results of the drug assays were that the stability of the representative drug was not impacted from contact with any of the syringe types when dispensed by the infusion pump. Three organic leachables were observed in this study above the reporting threshold. No non-volatile leachables were detected above the reporting threshold. For inorganic leachables, Calcium and Silicon were the most common inorganic leachable with Boron, Barium and Zinc also observed above the reporting threshold.

10:15 **Q&A**

10:30 ***Refreshment Break***

10:45 **Reporting Post-Approval Changes for Prefilled Injection Devices**
Dr. Michael Gross, RAC, Senior Consultant, Biologics Consulting Group
The reporting of post-approval manufacturing and design changes to NDA's and BLA's for pre-filled injection devices is a difficult regulatory problem since there currently are no regulations or guidance on the reporting of post-approval changes to combination product marketing applications. Predicate rules exist for reporting changes to drug, biologic and medical device marketing applications but how these rules apply to combination products is unclear. The Food Drug and Cosmetic Act, predicate rules and guidance documents describe what constitutes minor, moderate and major changes and the approval and timing required before manufacturers can implement change. But, how to apply these rules when these different medical product types are combined in a combination product is a complex problem, especially when the change occurs in the deviceconstituent part of a pre-filled injection system. The presentation discusses approaches that manufacturers may consider when applying existing regulations for the reporting of post-approval manufacturing and design changes to NDA's and BLA's for pre-filled drug injection devices.

11:45 ***Q&A***

12:00 ***Pre-lunch Exhibitor viewing***

12:15 ***Lunch***

FILLING & INSPECTION CASE STUDIES

1:15 **Future Oriented Processing of Nested Syringes and Syringe Filling**
Dena Flamm, Product Manager, Bosch
This session will cover fully automated lines with disposable filling systems, interchangeable fill systems and design for easy use within barrier systems to demonstrate flexibility. Aseptic transfer of nested syringes in pre-sterilized and bagged tubs into aseptic filling environment is much discussed due to residual risk of bag integrity. To make use of the increased quality with advanced aseptic processing in barrier systems the transfer of the syringes could be the weak link due to re-contamination of aseptic production environment with bioburden introduced via transfer of the tub. A variety of techniques to keep tub integrity during transfer or resterilization to the outside of the tub could be applied. Characteristics, benefits and disadvantages of common techniques are introduced.

2:00 **Final Quality Design of Pre-Filled Syringes**
Mike de la Montaigne, Eisai Machinery U.S.A. Inc.
The design and implementation of Cognex Vision Systems for pre-filled syringe defects on the final container, such as cracks, stopper defects, needle shield and flange area as well as innovative SD technology for clear solutions and X-ray technology for particulate matter in suspensions with be presented.

3:45 ***Refreshment Break***

3:00 **Customized Labelling Solutions for Injection Devices and Pre-filled Syringes**
Markus Bauss, Senior Sales & Project Manager, Global Key Account Management Schreiner MediPharm, LP
Pharmaceutical companies are faced with a changing environment when it comes to injection devices and pre-filled syringes. On the one hand, they have to serve the healthcare providers who administer the pharmaceuticals.

On the other hand, there is a growing trend towards patientself-injection. In addition, they have to cope with possible limitations in production efficiency due to the complexity and unique construction of the devices.
In an area where "platform" technology and late-stage customization are becoming a major element for the pharmaceutical industry, customized labels gain importance not only for the visual appearance but also for the functionality of devices and the patient's safety. Beside looking at the value-add of information and design by using labels the presentation will focus on new applications with pre-filled syringes & devices where the label offers functionality beyond that point. Improving grip of devices and patient information, ensuring patient safety, including tamper evident functionalities up to a fully label integrated device itself are topics that will be discussed during my presentation.
The objective is to create awareness for the impact which changes in technologies and processing can have on the production of injection devices and pre-filled syringes. Innovative labeling solutions can help improve productivity at the pharma manufacturer and also benefit the end-user through functional features that enhance convenience and safety when using the device.
By fulfilling our abstract objectives participants a) will be able to evaluate new trends in the market b) acquire knowledge about available customized labelling solutions and c) be aware of the options for tailoring them to market requirements and customer needs. Further, predicted reduced costs for pharmaceutical manufacturers ultimately help them to generate more revenue. A label supplier with proven solutions expertise and specialized know-how is a strong partner in development and marketing - for the wave of the future in injection devices and pre-filled syringes.

3:45 **The Relationship Between Silicone Layer Thickness, Free Silicone Oil and Protein Aggregation In Prefilled Syringes**
Markus Lankers and Oliver Valet, Rap.ID

Pre-filled syringes are because of their advantages of growing importance in the biopharmaceutical manufacturing. To ensure the smooth movement of the plunger on the inner surface of prefilled syringes silicone oils are usually applied to form lubricating films.
However, there are several issues related to the interaction of silicone oil and protein based formulations like the formation of particles through agglomeration and/or the absorption of the API in the silicon layer. Connecting these effects with the process parameters, of the siliconization itself, is difficult.
Up until now there is only a little knowledge about the of the protein and silicone oil interaction mechanisms. Also the possibilities to minimizing these effects by a optimized silicone layer in the syringes. In a laboratory study we investigated the interaction of silicone oil layers in pre-filled syringes and different protein formulations. Different amounts of silicone oil, transportation effects as well as baked on and spray on siliconization were taken into account in the design of this investigation. The quantification of the interaction will be performed with a new high sensitivity automated Particle Raman spectroscopic analysis equipment. The application of automated Raman spectroscopy delivers results on a statistical relevant level on thousands of identified particles. The recording of the silicone and protein signatures in the signal of a particle and the total number of their occurance in a sample is a strong marker to show the silicone oil induced agglomeration of proteins in the measured samples.
With the well control and characterization of the silicone oil layer and the usage of statistically meaningful particle identification we can link the influence of the siliconization parameters and the silicone agglomeration behavior of the drug. This approach enables the understanding of the siliconization process in order to minimize silicone induced issues for the manufacturing of precious biopharmaceutical products.

MANUFACTURING CASE STUDIES

4:15 **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.

- 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

5:00 **Pharmacopeial Control of Pre-filled Syringe Components and Good Distribution Practices**
Dr. Michael N. Eakins, Principal Consultant, Eakins & Associates

The three major Pharmacopeias (EP, JP, USP) all have chapters dedicated to the control of the three materials that are used in the construction of pre-filled syringes - glass, plastic and elastomers. Although there has been some movement towards alignment of requirements, considerably differences still remain. The presentation will compare the requirements in the three pharmacopeias and discuss recent changes to the USP and future directions for the control of these materials. The USP also has general information chapters that provide guidance on good storage and distribution practices for medicines and medical devices. This be be reviewed as it pertains to pre-filled syringes.

5:45 ***Close of Conference***

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