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PharmaED's

Pre-Filled Syringes Forum 2012

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

MARCH 15-16, 2012, 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
- Development Case Studies
- Manufacturing Solutions
- Visual Inspection
- Container Closures
- Stopper Movements
- Elastomeric Components
- Syringe Manufacturing
- Extractables & Leachables
- Combination Products

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Kiang Consultant Services
BD Technologies
Zeon Chemicals L.P.
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PFS Technologies
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Thursday, March 15, 2012

8:15 *Chairperson's Welcome and Opening Remarks*

FDA QUALITY SYSTEMS UPDATE

8:30 **Current State of the FDA Regulatory Framework for Quality Systems and Safety Reporting for Combination Products**
Michael Gross, Senior Consultant, Biologics Consulting Group
In 2009 FDA's Office of Combination Products issued two proposed rules, one on quality systems for combination products and another on safety reporting for combination products. FDA has received a considerable number of comments from the pharmaceutical and medical device industries through direct company and trade association commentary. FDA has indicated that it expects to issue the final rules around the end of 2011. This presentation will consider the current state of the regulatory framework for quality systems and safety reporting for combination products and will include a discussion of industry concerns expressed in comments and, if issued, a review and discussion of the final rules.

MATERIALS CONSIDERATIONS

9:15 **Future Materials for Pre-filled Syringe Components**
Patty Kiang, PhD, Kiang Consultant Services
Prefilled syringes are becoming a popular tool for sterile injectable drugs due to its ease of use, enhance of compliance, and reduce waste of expensive drug and marketing differentiation.
There are still some draw backs due to the breakage of glass barrel, silicon coating on inside of glass barrel causing protein aggregation, Tungsten vapor causing Protein degradation, rubber plunger leachable causing toxic effect etc. Due to all these reasons there is a definite need for better syringe construction materials and components.
A special clear plastic prefilled Syringe with Flurotec laminated rubber plunger, without silicone oil lubricant and Tungsten heated needle to eliminate leachable and protein aggregation concerns will be discussed.

10:00 **New Materials for Pre-filled Syringes**
Dr. Vincent J. Sullivan, Sr. Technology Manager, BD Technologies
Packaging of drugs in pre-filled syringes offers a number of advantages compared to the vial and syringe format. These include reduced drug wastage, improved accuracy of dosing and ease of use. The growing importance of pre-filled syringes in the pharmaceutical industry has led to a number of product innovations, including new materials for use in syringe components. The glass, plastic, lubricant and elastomeric components of pre-filled syringes can all impact drug product performance. In recent years, the stability of biopharmaceuticals in pre-filled syringes has become a topic of interest. New technologies have been developed to address these challenges. Topics to be covered in this presentation include:
- Packaging of silicone sensitive biotech drugs in pre-filled syringes
- New syringe materials, including plastics for pre-filled syringes (COP/COC)
- Future trends in pre-filled syringes

10:45 *Mid-morning Break*

10:45 **Exploring Future Materials for Pre-filled Syringes**
Toshiro Katayama, Product Manager, Zeon Chemicals L.P.
There are number of new Pre-filled Cycloolefin polymer (COP) device products in pipeline scheduled to be launched soon.While such products base is expected to expand at accelerated rate, ZEON continues to explore & develop new polymers suited for the medical device field.
The presentation will cover:
1) Key properties of current Medical Cycloolefin polymer (COP) grades, Regulatory Status and Bio-Compatibility, Protein Adsorption study, effect of Gamma/EB/Steam sterilization
2) Introduction of new products & technologies under development.

11:45 **Pre-filled Syringes – Update on Material and Quality**
Dr. Arno Fries, Director Product Management Tubular Glass, Gerresheimer
The question regarding the ideal primary packaging material for pharmaceutical products is discussed in the industry. Pre-filled syringes from cyclic polyolefin materials have been developed and are applied for specialty drugs and diagnostic agents. Glass syringes are used for the majority of heparins, vaccines and biotech products in the pre-filled syringe market. In this presentation, special focus is placed on the current discussion related to glass as raw material for syringes and other drug containers. The topics covered include:
- Trends in the pre-filled syringe market
- Pre-filled syringes from plastic and glass
- Glass as packaging material for syringes and vials
- Quality and durability of glass containers

12:30 *Luncheon and Exhibit Viewing*

1:30 **Innovations in Elastomer Components for Prefillable Syringe Systems**
Tibor Hlobik, Associate Director, PFS Technologies
Quality requirements for elastomeric closures continue to be refined and Pharma/Biotech companies expect suppliers to deliver safe and reliable products that minimize patient risk. New standards such as Quality by Design, automated inspection and steam sterilization for finished product are being applied to closures to meet

patient needs. A deeper review of specification trends, how suppliers are changing their development and manufacturing strategies and details of new innovative product solutions will be covered during the presentation. Several case studies will also be included that outline how cost of poor quality, impact of an extractables profile on drugs and poor syringe functionality can be reduced with proper selection of elastomeric products. The benefit of this information will be that packaging decision-makers fully understand material options when selecting syringe platforms and can mitigate potential quality risks during drug development through commercialization.

2:15 **Future-Oriented Processing of Nested Syringes, Syringe Filling: Pre-sterilized in Nest and Tub**
Dena Flamm, BOSCH

There is a significant growth in the need for administering drugs thru the use of syringes as well as the need for flexibility. 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 re-sterilization to the outside of the tub could be applied. Characteristics, benefits and disadvantages of common techniques are introduced.

3:00 ***Afternoon Break***

3:15 **Development of Syringeability Guide for Protein based Subcutaneous Formulations**
Liji Joseph, Senior Associate Scientist, Pharmaceutical R&D and Supplies, Pfizer

To study the syringeability of mimic protein solutions as a function of viscosity and needle size to enable development of syringeability guide for protein based formulations. This study provides guidance to formulators to attain a "patient friendly" injection (maximum glide force of 15-20N, </= 10s and with minimal needle gauge).
Methods: Different strengths of sucrose solutions were made in the viscosity range 1-60 cp to study syringeability. Three injection times (10s, 15s and 20s) with injection volume of 1 mL were tested. The syringe –needle system used was 1 mL BD plastic syringe with 3 needle gauges (26 G, 27G and 30 G) and 1/2" in length. An Instron 5500R instrument was used to measure the glide force. The Hagen-Poiseuille (HP) equation was used to calculate the glide force. The measured glide force was then compared with calculated glide force for each needle-syringe system for different injection times. Linear equations were derived from this study to predict the syringeability of protein based formulations.
Results: Glide force measured for solutions with viscosities < 7 cp was well below 15N, the acceptable criteria for force. The 30 G needles failed the patient friendly injection criteria of injection time ≤10s and glide force limit for solutions between 10 and 15 cp. For high viscosity solutions (>50 cp) both 30G and 27G needles failed the criteria. It was also observed that the calculated glide force using HP equation deviates from measured glide force for solutions with higher viscosities, less injection time (=10s) using thin needles (30G). For protein based formulations which were in the viscosity range of 4 cp – 36 cp, good agreement was obtained between the predicted and measured glide force values.
Conclusions: Based on the experimental data, obtained in this study and theoretical calculations using HP equation, the glide force can be predicted for given needle gauge and needle length to attain a "patient friendly" injection for a known viscosity formulation. The prediction will be less accurate if the solution viscosity is high (> 50 cp) injection time is reduced (< 10 s), and the needle diameter is small (30G).

PRE-FILLED SYRINGE CASE STUDY

4:00 **Pre-Filled Syringe Case Study – Determining Decision Factors for Extractables Studies and Testing Laboratory Service Providers**
A. Mark Trotter, Trotter Biotech Solutions

The growing use of polymeric materials utilized in Pre-filled Syringes has spurred new investigations into the question of extractable profiles and polymeric materials leaching into finished pre-filled Injectables products. This Case Study attempts to outline and review the necessary decision factors and testing parameters needing consideration when choosing an appropriate syringe and component materials.
These newer materials include for example, Cyclic Olefin Polymer (COP), Cyclic Olefin Copolymer (COC), fluoro-polymer and elastomeric components, e.g., plungers and tips. The advantages of these new materials making their use desirable may necessitate further investigation into extended stability studies using Arrhenius and Q10 assumptions /calculations , extractables and leachables (E&L) studies, and compatibility testing, when changing syringe and component base materials, e.g., glass , polypropylene, silicone.
We will examine the various stability, compatibility and E&L testing parameters required to meet or exceed Regulatory compliance and Industry standards. Additionally, examining the key decision factors such as analytical testing capabilities and analysis will assist in investigating and choosing an appropriate Contract Laboratory Organization (CLO.) The use of spreadsheets and matrices focuses on these key decision parameters resulting in more effective and efficient decision analysis.

4:45 **Evaluation of Silicone Oil Migration Post-Processing for Empty BD Hypak 1 ML Glass Syringes**
Don Eisenhauer, Research Investigator, Parenteral Products, Abbott
Siliconization of the glass syringe barrel and stopper is required for lubrication that assures proper syringe functionality both as a manual drug delivery device as well as when combined with an autoinjector. A collaborative Abbott and Becton Dickinson (BD) study was performed to track silicone oil content and distribution in empty syringes and to assess their impact on functionality in BD 1ML glass syringes from the time of application in manufacturing, through sterilization, until delivery to Abbott North Chicago, and during room temperature storage out to approximately eighteen months. To accomplish this, the silicone oil total content was determined utilizing a gravimetric solvent extraction method, the silicone oil distribution using interferometry, and syringe functionality with force testing. The syringe tub(s) were removed at selected points from the time of silicone oil application in BD manufacturing until received by Abbott. The joint study results provide an understanding of the changes that occur to the applied silicone oil layer and content in the empty syringe post-processing and during long-term storage at room temperature.

5:30 *End of Day One*

Friday, March 16, 2012

INSPECTION SOLUTIONS

8:30 **Inspection Solutions for Pre-Filled Syringes**
Peter Spinelli, Manager, Eisai Machinery U.S.A. Inc.
With the global market for pre-filled syringes as the primary parenteral drug delivery system reaching in the billions, there is an ever growing need for an effective inspection solution that can meet all of the demands. This case study will explain how advances in particle detection technology are being used to improve detection in suspension product, camera inspection techniques being used to reduce false positives due to bubbles, segmentation being used to detect small changes in product color or lighting techniques being used to detect hairline cracks. Modern design and inspection concepts, validation strategies are also presented and explained.

9:15 **Understanding the Impact of Latest Inspection Technologies for Pre-filled Syringes: An Overview and Discussion**
Patrick Schlatter, WILCO AG
This presentation shows how the latest inspection technologies are combined under one machine umbrella. These technologies consist of a stunning new approach using X-Ray to detect foreign particles and use the same technology to perform various component checks, such as testing for bent needles inside the needle shield. Together with a patented vacuum based integrity test or a laser based headspace analysis and a camera based cosmetic inspection, pre-filled syringes will have after these triple verification a quality signet. The lecture includes an insight into the technologies, provides test data from trials and shows actual machine configurations. A stability study performed together with an user will be presented as well including showing the necessary means for production safety.

- Latest Technologies Overview
- Combination of various technologies in one machine, resulting in cost savings, space reduction and reduced risk of glass breakages due to simplified product transfers

10:00 **Automated Visual Inspection System for Pre-Filled Syringe Plungers**
Damien Saleur, Technical Support Manager, STELMI
Evolution in the drug industry and the potential impact of certain defects in the appearance of pharmaceutical elastomer closures require the establishment of ever stricter quality specifications to meet the latest demands of pharmaceutical laboratories.
In the absence of a standardized frame of reference for appearance defects that is applicable to elastomer components for pharmaceutical use, the syringe component supplier has to identify the potential defects and can establish its own frame of reference, classifying them into categories from refusal defects to minor ones.
As visual quality is first of all the result of a total control of the manufacturing process, the frame of reference has to be associated with a specific production process to eliminate appearance defects at the source.
The following step then consists in installing visual inspection automatic machines at the end of production to control the components. These machines have to be specifically adapted to elastomer plungers and the potential defects identified.
In this presentation we will develop the integration of a 100% automated inspection system for plungers, demonstrating the efficiency of the process, and we will illustrate the impact on quality improvement.

10:45 *Exhibit Viewing and Mid-Morning Break*

11:00 **Impact of Formulation and Processing Parameters on Silicone Extraction from Cyclic-Olefin Copolymer (COC) Syringes**
Dipesh Shah, Ph.D., Research Scientist II, Baxter Healthcare Corporation
The effect of various formulation and process parameters on the extraction of silicone from siliconized COC syringes is reported. The impact of proprietary silicone curing process on COC syringe barrels was evaluated with respect to the rate and extent of silicone extraction. Similarly, the impact of formulation parameters such as pH, ionic species and co-solvents on silicone

extraction was also evaluated. The rate and extent of silicone extraction into contact solutions was inversely related to the degree of completion of the silicone curing process. The rate and extent of silicone extraction in solution were highest upon exposure to extreme pH solutions. The silicone extraction data indicates that the silicone curing process and formulation parameters have profound effect on the rate and extent of silicone extraction into solutions.

11:45 *Q&A with Conference Faculty*

12:00 *Exhibit Viewing and Lunch*

DUAL CHAMBER SYSTEMS

1:30 **Freeze-dried Products in Dual Chamber Systems – Why and How**

Andreas Rothmund, Vetter-Pharma

In the 'Basics' section, reasons for going 'dual chamber' will be explored, followed by an overview of current commercial systems. As part of this overview, the 'design space' of those systems, suitability information regarding substance classes and formulations as well as the basic process outline will be shared.
In the 'Specifics' section the major differences between vials and dual chamber systems will be highlighted before the focus is then placed on the freeze-drying step itself, where, using real-life data, factors affecting sublimation rates and moisture uptake will be explained.

On the way from lab-scale to commercial production, a set of analytical tools will be introduced that will support us in identifying the optimal freeze-drying cycle, as well as help us in analyzing potential process / product issues.

In the closing case study, some of the effects created by varying levels of silicone oil will be discussed.

2:15 **Development and Regulatory Strategies to Effect A Change from a Vial Presentation of a Drug or Biological Product to a Prefilled Injector Presentation**

Michael Gross, Senior Consultant, Biologics Consulting Group

This presentation will consider current technical and regulatory requirements and development strategies to effect a change from a vial presentation of a drug or biological product to a prefilled injector such as a prefilled syringe, auto injector, injection pen or microneedle patch. The presentation will consider submission strategies such as a new NDA or a sNDA CMC submission including the possibility of using a comparability protocol. The content of these submissions and acceptance criteria for product comparability will be considered. The use of pharmacokinetic bridging studies and human factors studies to validate the injector design will also be discussed.

3:00 *Afternoon Break*

PACKAGING SYSTEMS SOLUTIONS

3:15 **Plastic Packaging Systems for Parenteral Administration of Biopharmaceuticals**

Vinod D. Vilivalam, Ph.D.,Director of Strategic Market and Technical Development, Daikyo Crystal Zenith, West Pharmaceutical Services, Inc.

Newer biologics including mAbs are characterized by high doses and higher viscosities, which increases the chances of aggregation due to packaging systems. In addition, recent regulatory scrutiny of glass particles and delamination has added to the challenges to drug device combinations. These market factors have resulted in considerations of plastic delivery systems. The discussion will focus on a Daikyo Crystal Zenith plastic prefillable syringe systems, and cartridge based microinfusion system for large volume delivery. Attributes such as break resistance and the absence of silicone and tungsten, as it relates to drug storage systems for biopharmaceuticals will be discussed with appropriate case studies. The discussion will also include sterile CZ vials and bulk container systems that are proven to be effective for cold temperature storage for biopharmaceutical and cell therapy products.

4:00 **Pre-Filled Syringe Processing with RABS, Isolators, E-Beam & Alternatives and RABS & Total Room Decontamination with H2O2 Vapors**

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 vapor

4:45 *Q&A with Conference Faculty*

5:00 *Close of Conference*

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