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Pre-Filled Syringes Forum 2008

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

JUNE 5-6, 2008, SHERATON LA JOLLA HOTEL, LA JOLLA, CA

Featuring Case Studies and Lessons Learned from Industry Experts!

- **MATERIALS, DESIGN & CONSTRUCTION OF PRE-FILLED SYRINGES**
- **SAFETY CONSIDERATIONS & REQUIREMENTS**
- **NUMEROUS DEVELOPMENT CASE STUDIES**
Wyeth Pharmaceuticals Baxter Healthcare Corporation
Biogen Idec Amgen ...and more!
- **MANUFACTURING & FILLING SOLUTIONS**
- **REGULATION & INSPECTION OF PRE-FILLED SYRINGES**

Including Special Coverage On:

- **Syringe Plunger Movement**
- **Development Case Studies**
- **Tungsten Aggregation**
- **Visual Inspection**
- **Container Closures**
- **Stopper Movements**
- **Bubble-Free Filling**
- **Syringe Manufacturing**
- **Extractables & Leachables**
- **Combination Products**

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Eakins and Associates
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Optima Group
Vetter
Safety Syringes, Inc.
Amgen

West Pharmaceutical Services, Inc.
Ypsomed AG
Hyaluron Contract Manufacturing
Eisai Machinery
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Thursday, June 5, 2008**8:15** *Chairperson's Welcome and Opening Remarks***MATERIALS, DESIGN & CONSTRUCTION****8:30** **Design and Construction of Pre-filled Syringes**
Dr. Michael N. Eakins, Principal Consultant, Eakins and Associates

Pre-fillable syringes are now available in both glass and clear plastics such as cyclic olefins. The advantages and disadvantages of these two materials will be reviewed from the standpoint of both design and performance of pre-filled syringes. Pre-filled syringes and cartridges can be operated either manually or by power and auto-injectors. The effect of the mode of operation on the design of the pre-filled syringe will be considered.

9:00 **Understanding New Alternatives for Components and Systems for Pre-fillable Applications**
Fran DeGrazio, Vice President, West Pharmaceutical Services, Inc.

This presentation will cover syringe plunger and needle shield alternatives for conventional glass systems. The subject of silicone oil free COP systems designed specifically to address the needs of highly sensitive biotechnology products will also be covered.

- Ready to use film coated plungers
- Elastomer and rigid needle shield alternatives
- Vision inspected, silicone oil free, cyclic polyolefin syringe systems

9:45 **GMPs for Pre-filled Drug Delivery Devices**
Michael Gross, President, Chimera Consulting

The development and manufacture of a prefilled injection device is problematic due to uncertainty over how to appropriately apply different regulations for drugs, biologics and medical devices once combined into a single-entity combination product. Manufacturing quality regulations have not yet been established for combination products and it will be several years before these regulations are finalized. In the meantime only draft FDA guidance exists on the application of existing quality regulations to combination products. The guidance points out several places where compliance only with either the drug/biologic cGMP or the device QSR will not be sufficient to assure the quality of a combination product when the constituent parts are being combined and once they are combined. This presentation will provide analysis and interpretation of this draft guidance and recommend strategies for compliance with quality system regulations for drugs, biologics and medical devices.

10:15 *Refreshment Break***10:30** **Continuation of M. Gross Session****11:00** **Disposable Auto-Injector Markets, Functionality and Handling Considerations**
Ian Thompson, Head of Business Development, Ypsomed AG

The interest in auto-injectors for new biotech drugs is growing based on new pre-filled syringe based therapies. They provide additional convenience and are becoming standard in competitive self-injection markets e.g. for the treatment of autoimmune diseases. The presentation covers the following topics:

- Introduction to the market for auto-injectors
- Key functional features of disposable auto-injectors
- Syringe forces and their interaction with the auto-injector
- Handling and usability experiences

11:30 **Autoinjector Compatible Syringes**
Jeffri Johari, Senior Engineer, Device & Packaging, Amgen, Inc.

Rapid growth and increased competition in biotechnology industry are driving innovation in the delivery of injectable drugs. Autoinjector has evolved into the marketplace as one of the product presentations used in the marketplace. The syringe quality used in an autoinjector is vital to the performance of the autoinjector. Silicone oil distribution in a prefilled syringe is one of the key properties that plays a big role in the performance of the device. This presentation will discuss some of key syringe attributes for autoinjector including: (i) silicone oil Quantity versus Distribution versus Mechanical performance (extrusion force), & (ii) characterization of autoinjector compatible versus incompatible syringes.

12:15 *Pre-luncheon Exhibitor Viewing and Booth Presentations***12:30** *Luncheon Commences***1:30** **Safety Systems for Prefilled Syringes: The Past, Present, and the Future**
Christer Andreasson, Chairman and CEO, Safety Syringes, Inc.

The 1998 Sharps Injury Prevention legislation in California gave new life to needle safety technology, which until then had struggled to be adopted on a larger scale. This paramount milestone became further enhanced when Federal legislation in the United States was passed in November 2000. That provided companies such as Safety

Syringes, Inc. with the opportunity to promote its technology. A similar mandate—TRBA 250—became effective in Germany on August 1, 2007 and it is expected that other countries within EU will follow.

Today, safety systems for prefilled syringes are well accepted and a significant number of pharmaceutical companies have adopted this technology. While protection against needle stick injuries was the beginning, the safety system of the future will offer additional benefits such as protection against counterfeiting, will be used in combination with an autoinjector for self administration and will have applications for reconstitution of lyophilized drugs.

2:00

Syringes: Current Healthcare Worker and Patient Safety Issues

*Dr. Ross Sharp MB., Ch.B., FACS,
Inviro Medical Inc.*

The parenteral delivery of medication saves innumerable lives annually. In US hospitals the use of syringes also results in 800,000 needlestick injuries and some of the 100,000 deaths attributed to medical errors each year. Current legislation, regulations and guidance attempt to mitigate this toll by mandating safety technology for all syringes. OSHA, responsible for workplace safety, has recently released clarification on pre filled syringe compliance. The Joint Commission, the US hospital accreditation body has developed patient safety goals, including syringe labeling with patient identifiers.

Recent studies of current syringe designs by clinical experts and nursing organizations identified clinical preferences and deficiencies. Desirable anti needlestick and medication error reduction features were characterized. These studies are both a challenge and a competitive opportunity for pharmaceutical companies. Safety solutions for prefilled syringes and needles are available and others are in development. Pharmaceutical-syringe industry cooperation will be necessary for this next paradigm shift.

This session will:

- Discuss implications of OSHA clarification of anti-needlestick legislation
- Identify current clinical preferences
- Discuss Joint Commission goals on patient safety
- Present a joint ANA study on patient safety

DEVELOPMENT CASE STUDIES

2:30

In-Line Sterilization of Primary Packaging Components with Electron Beam Enabled Filling Isolators

*John T. Affourtit, Application Specialist,
Advanced Electron Beams*

Electron beam sterilization tunnels have become the de-facto standard for aseptic transfer of nested syringe tubs into filling isolators. Drug manufacturers are beginning to examine opportunities for leveraging this proven technology for direct in-line electron beam sterilization of primary packaging components. This approach eliminates the need for bulk sterilization of syringe tubs and orienting packaging components inside the isolator. Syringe barrels and stoppers are staged and oriented outside the isolator prior to transfer into the isolator. This approach compresses cycle time, removes process variables to validate and monitor, and reduces process complexity.

3:00

Refreshment Break

3:15

Suitability for Intended Use Considerations for Pre-filled Syringe Systems

Dennis Jenke, Ph.D., MBA, Senior Baxter Research Scientist, Technology Resources Division, Baxter Healthcare Corporation

Pre-filled syringe systems meet the regulatory descriptions for container closure and/or immediate packaging systems. As such, pre-filled syringe systems must meet the suitability for intended use guidelines, which include a consideration of:

- Protection
- Compatibility
- Safety
- Performance

Compatibility and safety considerations generally involve assessing the chemical interaction which occurs between the packaging system and its contained drug product. Given the nature and application of pre-filled syringe systems, direct safety issues may be somewhat reduced versus other packaging systems used in pharmaceutical applications. However, indirect safety and compatibility issues may be exacerbated in such systems. The potential for chemical interactions in pre-filled syringe systems will be examined and reported cases of such interactions will be discussed.

This presentation will consider the following aspects of the suitability for use requirements:

- Typical leachables/extractables associated with pre-filled syringe systems

- Potential direct safety issues associated with such leachables; toxicological risk assessment considering safety thresholds
- Examples of indirect safety issues associated with pre-filled syringe systems
- Interactions between the active ingredient and the syringe materials as a primary driver of product viability
- Examples of syringe/drug interactions

3:45

Case Study: Sterilization of an Aseptically Filled Biopharmaceutical Utilizing Hydrogen Peroxide Low Temperature Gas Plasma

Mike Valentine, Director S&I Business, Johnson and Johnson Advanced Sterilization Products

Discussion will center around the challenges of delivering an aseptically filled biopharmaceutical in a sterile package. Main focus of this presentation is the use of hydrogen peroxide low temperature gas plasma sterilization modality, in an adjunct process, to sterilize the exterior of pre-filled syringe and packaging. This is accomplished without compromising aseptically filled drug thus preventing cross contamination issues during aseptic process and from the user to the patient. Investigation of available sterilization technologies, advantages and disadvantages of each sterilization modality will be discussed and why the hydrogen peroxide low temperature gas plasma method should be investigated for this application. An overview of the hydrogen peroxide low temperature gas plasma sterilization technology will be given along with details of feasibility testing, cycle development and validation of the process.

4:30

Elastomeric Pre-filled Syringe Components for the Future

Renaud Janssen, Ph.D., Technical Support Director, Helvoet Pharma

This presentation will address the following topics:

- The need for compatibility of rubber plungers with WFI called for low extractables/ low leachables materials
- Irradiation sterilization emerged as sterilization method. Irradiation sterilization as opposed to steam sterilization imposes different requirements on the behavior of prefilled syringe plungers. Chemical and physical effects of irradiation on prefilled syringe plungers are illustrated
- For needle sheaths and tip caps market requirements have led to the phase-out of natural rubber as elastomeric base material.

5:15

Close of Day One

Friday, June 6, 2008

8:15

Chairperson's Day Two Opening Remarks

8:30

Syringe Manufacturing and Innovation

Patrick Grueninger, Manager, SCHOTT

The manufacturing process of a pre-fillable syringe is very complex and far beyond the ordinary glass container production. Only the best raw material, with the finest quality, in dimensional and cosmetic aspects, is able to provide a suitable starting point. The production of the glass barrels requires highly skilled personnel combined with state of the art converting machines. After this first step, bulk syringes are either sold directly to the customer or are being processed to a RTFS. The bulk syringes which stay in the process are being washed, siliconized and assembled before ETO is used to sterilize the product.

The market is moving towards much more complex drugs than in the past. These drugs provide customers easier treatments and therefore more quality in their lives. Innovations in the packaging section help to safely store these high potential drugs. New needle systems and advanced coating technology are examples of such improvements.

9:15

From Vial to Dual-Chamber System: Advantages and Key Considerations

Andreas Rothmund, Vetter Pharma

Dual-chamber systems offer significant advantages over 'vial plus diluent' presentations. If choosing the dual-chamber approach already in development or as part of life-cycle management certain development steps are imperative. This talk is going to take you on a tour through the ups and downs of a real project.

Starting from a comparison of the existing to the target system and the resulting process differences the necessary development steps will be addressed.

- Theory: the motivation and major differences between dual chamber syringe and vial
- Components and process
- Points to consider
- Developmental approach for a real product, including phases and milestones
- Conclusions

REGULATION OF PRE-FILLED SYRINGES

10:00

Regulation of Pre-Filled Drug Delivery Devices

Michael Gross, President, Chimera Consulting

This presentation will review the current state of regulation of prefilled drug delivery devices with emphasis on development, registration and post-approval requirements.

It will consider how to reasonably comply with current regulations for drugs, biologics and medical devices in the absence of specific regulations for combination products and the existence of only limited guidance.

10:30 *Refreshment Break*

MANUFACTURING & FILLING

10:45 **Microbiologic Contamination in Pre-Filled Syringes: Influence of Choice of Stopper, the Gas Bubble Size and Reduced Atmospheric Pressure**

Shawn Kinney, PhD, President, Hyaluron Contract Manufacturing (HCM)

The advantages of Bubble-free or reduced bubble filling of syringes have been demonstrated. These advantages include:

1. Reduction/elimination of stopper movement in reduced atmospheric pressures during shipment
2. Enhanced stability profile of oxygensensitive compounds
3. Enhanced stability profile of certain protein products that rearrange themselves at gas-liquid interfaces
4. Improved accuracy and precision of delivered dose
5. Creation of an unfavorable environment for the growth of aerobic micro-organisms

A sterile barrier is created where the stopper is in intimate contact with the glass barrel of the syringe. The sterile barrier spans the total distance from the upper most to the lower most point of stopper contact. We call this parameter the sterile barrier height, Hsb.

A gas bubble, such as that left in a syringe, can act like a spring, it can be compressed and it can expand. If the bubble inside a syringe expands, it causes the stopper in the syringe to move. This could occur whenever the external temperature or ambient pressure change. When the pressure or temperature returns to its original condition the stopper will return to its original position, leaving no apparent evidence that it had moved.

The movement of a stopper, due to expansion of the gas bubble inside may potentially cause a sterility failure if the stopper moves greater than Hsb. Once the stopper has moved more than Hsb, it may pull micro-organisms or contaminants back into the drug product when the stopper returns to its original position. This same effect could occur if a stopper moves multiple times less than Hsb, where the sum of all of the stopper movements exceed Hsb. In this presentation it is shown that the size of the gas bubble, the pressure of the reduced atmosphere and

Hsb will determine if there is a potential sterility breach from stopper movement. Given a stopper choice and the reduced pressure that a pre-filled syringe would be exposed to, the acceptable size of a gas bubble from the filling process can be calculated.

Additionally we demonstrate that a gas bubble leads to a tip cap/needle sheath removal product drip which decreases the precision and accuracy of dose delivery. The product drip and precision is improved by reducing or removing the gas bubble.

11:15 **Market Trends in Processing Pre-Filled Syringes: A Machine Manufacturer's Point of View**
Matthias Poslovski, Technical Sales Director, Optima Group Pharma

When planning a new processing line for pre-filled syringes more and more pharmaceutical companies tend to send following questions to the machine manufacturer:

- How to debug (manual / automatic)
- How to delid / deline (manual / automatic)
- What kind of filling technology to use (rotary piston pumps vs. time-pressure dosing)
- What kind of plunger insertion method to use (vacuum vs. mechanical)
- How to make fill weight checks (off-line, fully automatic)

In the presentation, various methods will be presented in addition to current market trends of each individual issue.

11:45 *Luncheon*

1:00 **Investigation of Particulate Issues in Pre-filled Syringes**

Chanel K. Yee, Gianni Torraca, Colin Cao, Gary Li, Wendy Jing Zai-qing Wen, Formulation & Analytical Resources (FAR), P & PD, Amgen Inc.

Particulates found in protein pharmaceutical products in pre-filled syringes (PFS) have been an increasing concern in the biopharmaceutical industry as particulate-related problems could potentially lead to clogging and injection failure in syringe products. Therefore, rapid isolation and identification of these unknown particulates are important to the investigation of particulate formation. Various classical and advanced analytical techniques, including optical microscopy, FTIR microscopy, scanning electron microscopy and energy dispersive X-ray spectroscopy, are currently used in our lab for accurate particulate identification. Here in this presentation, several investigations regarding particulate issues in PFS are briefly reviewed. These cases serve to highlight the challenges and the diversity of particulate incidents found in PFS products.

1:45

Tungsten, Pre-Filled Syringes and Protein Aggregation

Rob Swift, Senior Principal Engineer, Drug Product & Device Development, Amgen, Inc.

In the manufacture of glass pre-filled syringe barrels, tungsten pins are a common tooling material around which the fluid path and needle channel are formed at the tip of the barrel. Recently, Amgen has learned quite a lot about the potential for tungsten residue from this process to trigger protein aggregation - in some cases at levels less than 1 part per million. This talk describes the efforts of Amgen and our syringe supplier to characterize and control tungsten deposition during the forming process and tungsten removal by rinsing. This work also required a clear understanding of the effect of the fill - finish process on the exposure of drug product to tungsten. This, in turn, led to the development of a novel extraction procedure and analytical method to quantify residual tungsten in the barrels. Finally, the talk will discuss methods developed by Amgen to assess the sensitivity of therapeutic proteins to tungsten.

INSPECTION OF PRE-FILLED SYRINGES

2:30

Current Methods for Inspecting Pre-Filled Syringes

Mike De La Montaigne, President, Eisai Machinery

Prior to labeling and final packaging, an important step in the process of manufacturing pre-filled syringes is "Inspecting" syringes for various defects, such as Particulate Matter (PM) and / or cosmetic defects such as cracks in the glass, liquid in the plunger, missing cap or bent needle, etc. This presentation will cover:

- Methods used for inspection.
- Current and future technologies, as well as the number of inspections required to accurately perform a quality inspection process

3:00

Improved Equipment for the Manufacturing of Glass Syringes: A Cooperation Project

Howard Drake, VP Sales, Ompi of America

This case study presentation will feature the development of a fully renovated glass syringe manufacturing equipment process focused on highly efficient devices and innovative solutions.

Main project steps and key communication strategies employed especially during the commissioning and process fine tuning operations phases will be covered.

3:30

Refreshment Break

3:45

Filling Line Isolator With E-Beam for Pre-Filled Syringes

Jim Spolyar, Technical Director, SKAN US, Inc.

This non-commercial presentation will highlight recent "state-of-the-art" aseptic processing lines that have been installed for pharmaceutical syringe filling around the world, including sites at GlaxoSmithKline (Germany), Janssen (Belgium), Sanofi-Aventis (France), Novartis (Switzerland), and Amgen (USA).

- Review the isolator and E-Beam design features and latest developments
- Review customer experiences in choosing isolators over a traditional clean room or Restricted Access Barrier System (RABS)
- Review the project schedule and any challenges that were encountered, while getting each system installed, validated and in operation.

4:15

Evaluating Proper General Trends for Autoinjectors and Pre-Filled Syringes

Dr. Carl Hitscherich, Pharmaceutical Process Development, Biogen Idec

This talk will discuss the development of combination products. In particular an overview of development activities required to develop commercial dosage forms that will be marketed as prefilled syringes and/or as combination products (Autoinjector) will be discussed. Each stage of development will be presented utilizing case studies.

The talk will highlight development activities related to:

- Primary container closure selection
- Strategies for siliconization
- Development of an autoinjector that is compatible with the prefilled syringe selected.
- Strategies for validation

5:00

Close of Conference



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