PharmaED’s

Pre-Filled Syringes Forum 2008

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

JANUARY 17-18, 2008, RADISSON-PLAZA WARWICK, 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

Wyeth Pharmaceuticals
Amgen, Inc.

Baxter Healthcare Corporation
Biogen Idec

…and more!

• MANUFACTURING & FILLING SOLUTIONS
• REGULATION & INSPECTION OF PRE-FILLED SYRINGES

Plus Special Session!

Use of Pre-Filled Syringes Within the Industry: Past, Present and Future Requirements on Parenteral Drug Delivery System Units

Thomas Schoenknecht, Head of PDA Prefilled Syringe Interest Group and Director, Drug Product and Device Development, AMGEN, Inc.

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MATERIALS, DESIGN & CONSTRUCTION

8:45 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.

9:15 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

10:00 Use of Pre-Filled Syringes Within the Industry: Past, Present and Future Requirements on Parenteral Drug Delivery System Units
Thomas Schoenknecht, Head of PDA Prefilled Syringe Interest Group and Director, Drug Product and Device Development, Amgen, Inc., Former Director Product Development/Product Management, Gerresheimer PharmaSystems
The presentation will highlight the development of pre-filled syringes from the beginning to the current status. Requirements of specific therapeutic classes (anticoagulants, vaccines, biotech) on syringes and drug delivery devices will be presented and future developments in the area of injection systems will be highlighted.
- Understand the material and configuration available
- Overview of accessories for syringes
- Specific requirements of given therapeutic classes on syringes
- Discussion on siliconization and alternative coatings

SAFETY CONSIDERATIONS

11:45 Safety and Self Injection Devices for Pre-fillable Syringes: Key Requirements for an Appropriate “System” Approach
Karim Bennazzouz, European Marketing & Business Development, BD Medical - Pharmaceutical Systems
Pharmaceutical companies are choosing more and more devices that need to be combined to drug primary containers in general and more specifically to glass pre-fillable syringes.
When doing so, many important questions must be considered:
- How does one choose the most appropriate delivery system?
- What are the most critical elements of the decision matrix?
- How to make trade-off decisions?
- Are trade-offs even necessary?
- How to weight each decision criteria?
- What’s important and what is minor?
These and other important questions will be addressed through the presentation.
### Development Case Studies

#### Syringe Plunger Movement During Air Shipments
**Jerome Olivas, Principal Packaging Engineer, Wyeth Pharmaceuticals**

During air shipments (or ground transport through areas of higher elevation), filled syringes will be exposed to atmospheric pressures typically lower than the syringe-filling site. The plunger position will be in a state of equilibrium that is based on the syringe’s original internal headspace pressure at filling and the current ambient air pressure during transport. Consideration of original plunger placement and headspace should be given for:

1. Potential breach in sterility by the plunger moving into a non-sterile portion of the syringe barrel.
2. Impact of the final plunger position with regards to subsequent downstream (e.g., plunger rod insertion) processing.

This presentation will examine the physics associated with exposing filled syringes to different atmospheric pressures. Experimental results will be discussed that demonstrate the effect of headspace volume, atmospheric pressure, and syringe type on plunger movement. Also to be discussed are results demonstrating plunger placement accuracy and the corresponding issues with plunger rod insertion.

#### 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:

- Protection
- Compatibility
- Safety
- Performance

Compatibility and safety considerations generally involve assessing the chemical interaction which occurs between the packaging system and its contained drug.

### 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.

### 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
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

4:15 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.

5:00 Improved Equipment for the Manufacturing of Glass Syringes: A Cooperation Project

**Paolo Golfetto, R&D Manager, Glass Division, Nuova Ompi**

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.

Friday, January 18, 2008

**Chairperson’s Day Two Opening Remarks**

**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.

**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
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.
A rapid, nondestructive approach for empty or pre-filled syringe integrity testing is proposed using vacuum decay methodology described in international testing standard ASTM 2338. Test methods and data are presented demonstrating the ability of vacuum decay to identify visible to subvisible defects. No package preparation is required and the test is completely nondestructive. ASTM 2338 is recognized by the FDA as a consensus standard.

Refreshment Break

Sensitive Drugs and Prefilled Syringes: Emerging Trends and Technologies
Justin Wright, Ph.D., Senior Chemist, BD Medical – Pharmaceutical Systems
BD’s Sensitive Drug Initiative is a forward-looking effort aimed at developing novel and appropriate technologies to meet the current and future needs of the biotechnology industry. Significant progress has been made within BD to optimize existing prefilled syringe solutions and to develop the next generation of highly compatible prefilled syringes.

For each primary component of a prefilled syringe, BD has robust and active programs in place, which describe the nature of the potential interaction and methodologies needed to minimize risks. Current solutions and emerging technologies for the prefilled syringe marketplace will be presented.

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

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