

2017 Pre-Filled Syringes Forum:

Strategic Development, Safety & Regulatory Compliance,
and Commercialization of Pre-Filled Syringes
April 10-11, 2017, Racquet Club of Philadelphia, PA

Featuring Lessons Learned and Case Studies From Industry Experts:



Jonathan Amaya-Hodges
Senior Manager, Biogen



Nicholas Zampa
Scientist, Pfizer



Diane Doughty
Senior Scientist,
MedImmune



Edmond W. Israelski
Consultant, Retired Director
Human Factors AbbVie



Galen Shi
Group Leader,
Eli Lilly & Co.

With the Pre-Filled Syringes market expected to top \$16 billion dollars by 2021, the industry is looking for next generation materials, technologies and production strategies to streamline commercialization and to adapt quickly to a changing regulatory environment. Pharma Ed Resources, an industry leader since 2004, in delivering market-driven research on PFS, is proud to announce its **2017 Pre-Filled Syringes Forum**. Pharma Ed brings together top scientists, regulatory experts and innovators to share best practices and the latest research in this field, enabling you to maximize your organization's leverage in this dynamic and growing market.

Including Special Coverage On:

- Key Factors in Combination Product Development: Regulatory Hurdles in Receiving PFS and Pen Approvals for Human Factors Studies
- Patient Centric Designs For Pre-Filled Syringes
- Next Generation Materials & Design of Pre-Filled Syringes
- Improving Quality, Connectivity, and Cost Control in Combination Products & Autoinjectors
- Smart Devices: Their Emerging Role in Auto-Injector Systems
- Sterile Manufacturing of Injectables at CMO's
- Extractables case study of resins HDPE, TPU & PEBAX
- Managing the Materials used to Construct Pre-Filled Syringes—Selection and Supply Chain Control
- Latest Market Trends and Needs for PFS
- Overcoming Complex Requirements for Biologic Drug Delivery

Featuring Representation From:



Monday, April 10, 2017**7:30** *Complimentary Breakfast***7:50** *Welcome and opening remarks by Chairperson: Michael Eakins, Principal Consultant, Eakins & Associates, Inc****Critical Issues—Examining the Regulatory Environment for Pre-Filled Syringes & Combination Drug-Delivery Systems*****8:00** **Demystifying the PFS Space from a Global Regulatory Perspective*****Darin Oppenheimer, PhD, Regulatory Affairs Director for Medical Devices and Combination products, Merck***

- Evaluation of the current trends in industry
- Identification of Global Regulatory Challenges regarding pre-filled syringes and regulatory submissions
- Best practices for PFS regulatory filings
- Advantages and Disadvantages of the Pre-filled Syringe Approach and Potential Pitfalls

8:40 **Quality and Regulatory Affairs Best Practices for External Partnerships in Combination Product Development*****Jonathan Amaya-Hodges, Senior Manager, Regulatory Affairs, Biogen***

Combination products, particularly drug delivery systems, are becoming more prevalent with the increasing need for both product differentiation and ease of use for patients. These systems are often developed in partnerships between a biotechnology or pharmaceutical company and a device designer/manufacturer, and with the implementation of the combination product rule in the US (21CFR4), an effective working relationship between those parties becomes essential, particularly in Quality and Regulatory aspects. This presentation will highlight best practices in these areas including how companies can move beyond minimum compliance in order to establish and maintain an efficient, responsive, and mutually beneficial partnership for developing and supplying drug delivery combination products, including pre-filled syringes and auto-injectors.

9:20 **Key Factors in Combination Product Development: Regulatory Hurdles in Receiving PFS and Pen Approvals for Human Factors, Studies*****Dr. Edmond Israelski, Consultant, Retired Director Human Factors AbbVie***

The US FDA continues to raise expectations for robust Human Factors Engineering in the design and evaluation of Combination Products. The presentation will cover what these expectations are including:

- Final CDRH HF Guidance on the medical device part of the combination product.

- FDA recognition of IEC and ISO Usability Engineering Standards and AAMI Standards that are relevant
- Draft Combination Product HF Guidance from FDA CDRH/CDER/OCF
- Final FDA CDER DMEPA Guidance on Minimizing Medication Errors
- New Draft FDA Guidance on HF comparative Studies needed to show interchangeability of drug delivery systems for biosimilars.

Each of these standards and guidances will be covered as well as some of the inconsistencies that industry has observed among them.

10:00 *Mid-Morning Coffee & Networking Break***10:25** **A Cautionary Tale About Injection Pen Human Factors Research Gone Bad*****Joely Gardner, PhD, Usability Testing Expert, FDA Regulatory Consultant, Cal State Fullerton, Human Factors Research***

Not all human factors research is good research and applications have been denied because of “bad” research. This presentation will discuss a case study of injection pen human factors research and the elements that differentiate between well-designed and poorly-designed and executed studies.

This presentation will cover:

- A case study of an injection device usability trial that failed miserably
- Warning signs of an inadequate human factors study
- The practical differences between formative and summative usability research
- How to maximize the actionable data from formative studies
- How to prepare for usability trials to facilitate a successful outcome
- How to decide what must be tested
- Cautions about inclusion/exclusion criteria for recruiting participants

11:05 **Enabling a Patient-Friendly Design: Robust Design Control for Connectivity of a Co-Packaged Combination Product*****Nicholas Zampa, Scientist, Formulation and Process Development—PhRD—Biotherapeutics PharmSci, Pfizer (Contributing Authors: Sarah Weiser; Ling Lu, PhRD, Biotherapeutics Pharm Sci., Pfizer, Inc., Andover, MA)***

Pfizer developed a co-packaged combination product consisting of a luer-lock WFI pre-filled syringe (PFS) and a luer-lock needle which is assembled to the PFS by the user at the point of use. Initial design requirements were generated from an assessment of the ISO syringe standards, and close collaboration with component suppliers. The result was a co-packaged combination product design that can be divided into distinct design levels. Each design level provides a point of control and an opportunity for verifying connectivity during design verification.

The relevant design levels include 1.) the individual components—needle, syringe barrel and luer-lock adapter (LLA), 2.) the sterilized subassembled syringe—LLA assembled to the syringe barrel, and 3.) the PFS + needle assembly—syringe with attached finger-grip, plunger rod, and needle. Design verification at the component level leveraged ISO standard compliance information from the bulk syringe and LLA vendors. Design verification at the sterilized sub-assembled syringe combined information from Pfizer manufacturing division and component vendors. Design verification of the PFS + needle assembly relied on bench-top laboratory testing.

Design verification across design levels requires a plurality of design verification strategies. The end result is a safe, effective and user-friendly co-packaged combination product that is capable of accurately delivering the required volume of the enclosed drug to the patient. This example of dividing the combination product into distinct design levels and enlisting a multitude of design verification methods to address each level, highlights a paradigm for robust design control and verification.

11:45

CASE STUDY

COP Technical Data Update

Shotaro Suzuki, Manager, Zeon Chemicals

This presentation will provide an update and recent case study on COP, an innovative polymer widely used in the PFS industry. Topics to be covered include:

- Key properties and features of COP & its benefits for pre-filled syringe applications
- Mechanical properties after exposure to gamma, steam, EOG and cryogenic temp
- JP, US, EU Pharmacopoeia and ISO 10993 status
- Extractable/leachable test data in COP syringes with various chemicals
- Protein adsorption/aggregation study data with actual protein drugs to COP vs. glass
- Delamination study data on glass syringe

12:15

Complimentary Lunch & Networking Hour

Technology Spotlight—Considerations for Patient-Centric Designs

1:15

Determining User-Relevant Requirements for the Development of Combination Products

Diane Doughty, Senior Scientist, Drug Delivery & Device Development Group, MedImmune

Design input is defined in 21 CFR 820 as the physical and performance requirements of a device that are used as a basis for device design. Regulatory guidances and industry standards provide much direction in defining the technical requirements for prefilled syringes and other needle-based injection systems. However, the intended use of the device and the capabilities of the intended user must also be considered. The development of prefilled syringes and other devices for delivery of viscous formulations and dose volumes exceeding 1 mL places additional focus on generating user-relevant design input requirements. This presentation

1:55

Patient Centric Designs For Pre-Filled Syringes

Tiffany Kay McIntire, Human Factors Engineer, Eli Lilly & Co.

This presentation will address several topics that are central to advancing user-friendly designs in next generation PFS technologies. These will include:

- Understanding Human factors evaluation methods in order to achieve optimal design
- Empowering and involving patients—the role of patient-centred model in drug delivery
- New materials and modifications to existing materials—their impact on quality and reliability

2:35

Afternoon Coffee & Networking Break

Industry Spotlight—Examining Key Market Trends and Needs for Development of Next Generation PFS

3:00

Pre-Filled Syringes: Trends and Market Needs

Joel Cotten, Director, Aptar Pharma

The prefilled syringes market is evolving with different dynamics than in the past. We propose to review these novel trends and market needs.

Prefilled syringes were developed originally to face market demands coming from the small molecules and the vaccines markets. Today we acknowledge new market needs coming from markets as various as the biotech and the medical devices market. We propose to describe the dynamics of these four markets and to present how these various demands affect the definition of the prefilled syringe and its different components (elastomers and active secondary packaging).

The presentation will encompass the pharmaceutical needs, the user needs, the process needs, the new products development and the quality expectations in this emerging market. Finally we will show with examples how prefilled syringes design is evolving with regards to these new market requirements.

3:30

Development Strategies for Prefilled Drugs Intended for Self-Injection

Tibor Hlobrik, Director, Global PFS Platform, West Pharmaceutical Services

Many drugs in development are being targeted for self-administration using a prefilled syringe and cartridge in a custom device for increased compliance. Selecting the right container and device combination is crucial to ensure high-quality treatments with better patient outcomes. This session will discuss strategies being applied by pharmaceutical companies for product selection with technical examples for a range of drug product applications, including high volume and through consideration of unique user requirements.

4:00

Considerations for Selecting Drug Delivery Systems**Jianxiu Zhao, Staff Engineer, BD Medical, Pharmaceutical Systems**

The requirements for biologic drug approval continue to grow, with an overall aim to improve patient safety, experience and health outcomes while managing cost. With increased competition, defining drug development strategies which properly consider the delivery system is critical to a program's success. This session will cover technical considerations and testing strategies to optimize the selection of delivery systems and prove their suitability, compatibility, and performance with the drug as a combination product.

Panel Discussion

4:30

What's Next in the World of Pre-Filled Syringes? Re-imagining an Industry Paradigm

Members of the audience will set the agenda in this open forum discussion of the current state and future of PFS and related injectable devices.

Moderator:

Michael Eakins, Eakins & Associates

Panelists:

Edmund Israelski, Consultant, Retired Director
Human Factors AbbVie

Padam Sharma, Teva Pharmaceuticals

Nicholas Zampa, Pfizer

Darin Oppenheimer, Merck

5:00

*Close of Program Day One***Tuesday, April 11, 2017**

7:30

Complimentary Breakfast

7:50

*Chairperson Remarks: Michael Eakins, Principal Consultant, Eakins & Associates, Inc***Technology Spotlight—Autoinjectors: Smart Device Interfacing & Systems Development Approaches**

8:00

Trends in Self-Injection: Large Volume Autoinjectors, Wearable Devices, Connectivity in Self-Injection**Jakob Lange, PhD, Director Delivery Systems, Ypsomed**

The pharmaceutical market is constantly changing and pharma companies around the world have to adjust to the pace of changes to be successful. The last decades have been characterized by the development of reusable pens as well as disposable pens and autoinjectors, all of them highly precise mechanical systems. Today the market is on the cusp of introducing next generation devices that are connected and to include complex electromechanical

8:45

CASE STUDY

Systems Integration of Drug, Prefilled Syringe and Autoinjectors**Galen Shi, Ph.D., Leader of Autoinjector System Engineering, Eli Lilly & Co.**

The author will present case studies of autoinjector failure modes, and highlight the importance of understanding drug/packaging/device interactions and the need for systems development approach. The biotech industry is facing a significant opportunity in integrating drug and device in developing combination products, and yet we often encounter interface issues that are not fully vetted in the product design phase. The audience will get a glimpse of the relationship between drug product attributes and prefilled syringe performance, as well as impact to device functionality. Systems development approaches will be showcased.

9:30

*Mid-Morning Coffee & Networking Break***Materials Selection in PFS for Biologics**

9:55

Siliconized Syringes: Analysis of the Quality and Stability Testing**Olga Laskina, Ph.D., Application Scientist, rapID**
(Contributing authors: **Oliver Valet, Markus Lankers, rapID**)

Silicone oils are applied to the inner surface of syringes to form lubricating films. The uniform distribution of the silicone layer in prefilled syringes guarantees the consistent injection of the drug. On the other hand, protein based therapeutics can have strong interactions with the silicone oils used in prefilled syringes. Excess of silicone or its non-homogeneous distribution can induce protein aggregation in formulations. The formation of protein aggregates is highly unfavorable as it can cause undesirable immune responses resulting in reduced efficacy and even life threatening autoimmunity.

In this presentation we will go over the basics of the siliconization process and will discuss the relationship of different silicone application methods with homogeneity and thickness of silicone layer. We will discuss several methods of silicone layer characterization including the Layer Explorer (LE) instrument. LE is an automated device that measures layer thickness within the inner surface of a syringe and generates a map of the silicone oil. We will show examples of silicone thickness and distribution and demonstrate how LE can be used to determine the quality of siliconization in syringes. We will discuss the impact of silicone oil on syringe performance as well as on long-term stability of protein-based formulations. Finally we will demonstrate an integrated approach to analyze formation of silicone-induced protein agglomerates.

10:40

Integrated Approach to Filling Technology Selection Needs and Challenges for a Pipeline of Antibody Drug Candidates from Monoclonal Antibodies to Oncolytics Utilizing Containers Ranging from PFS, Vials, Cartridges to Custom Containers

Nan Yung Lin, MS, MBA, Drug Product Technology

This presentation covers the planning for aseptic filling equipment selection in a multi-biologic/sensitive drug pipeline environment from large volume injectable to standard sub-cutaneous drug delivery. To support a robust pipeline with limited manufacturing space, multiple highly flexible filling systems capable of processing multiple container formats and sizes are necessary. Some attributes and criteria include:

- Primary container type, size and format
- Biologic properties and equipment interactions
- Space and location constraint
- Drug product scalability, transferability, process-ability
- Speed to commercialization

We evaluated multiple attributes to objectively filter through multiple flexible filling systems down to two top “flexible filler” recommendations best optimized for our needs.

11:25

Characterization of the initial level and Migration of Silicone Oil Lubricant over time in Prefilled Syringes for Biologics using Layer Explorer and ZebraSci Technologies

Liji Joseph, Scientist, Pfizer
(Contributing authors, Anjali Mehta, Hilbert Billones, Kirk Roffi, Lisa Rising, Mike Koby)

Borosilicate glass Prefilled Syringes (PFS) have become one of the most commonly used devices for the delivery of therapeutics in parenteral formulations. In particular, auto-injectors preloaded with PFS facilitate the convenient and efficient self-administration by patients. Polydimethyl siloxane, or Silicone oil, is used as a lubricant in PFS to facilitate the smooth motion of the plunger during injection. In this work we demonstrate the application of two techniques including thin layer interference reflectometry (layer explorer) and zebra optical system (zebraSci technologies) to visualize and characterize silicone oil amount and distribution in PFS stored at different orientations (tip up, tip down and horizontal) over time at accelerated (40°C) and real time temperature conditions (5 and 25°C). The results showed that silicone oil migration happened over time for empty as well as filled PFSs stored at different conditions. Non-uniform silicone oil coating in a syringe barrel plays an important role in the quantitation of silicone oil by interference reflectometry. An insufficiency of the amount of silicone oil in the barrel of the PFS can cause significant changes in the functionality testing. This work provides valuable data on use of both techniques in selection of initial silicone oil target as well as monitoring changes to silicone oil distribution in PFS over time.

12:10

Complimentary Lunch & Networking Hour

1:15

Innovations Leading to Improvements in Patient Onboarding

Paul Sullivan, Associate Director, Noble

Self-injection above other applications and therapies has taken the forefront as more patients are challenged to take their own health into their hands. With multiple studies suggesting factors such as needle anxiety and confidence affecting patient onboarding along with pharmaceutical companies incorporating safety mechanisms and shields to not only protect the user from undo needle puncture but also calm the fears of users. Through these insights it has become apparent there are issues when it comes to a user self-injecting with in some extreme cases the very sight of a needle may prevent a patient from being adherent to therapy.

Classical conditioning studies has shown that experiences and familiarity changes behavior. Although generic in terms, Pavlov's dog learned to salivate by the sound of a bell and beyond animalistic instincts the blind learn to read and venture to new surroundings and the deaf learn to communicate and be heard. With the progression of time comes evolution in ideology and innovation in the pharmaceutical industry. Since the emergence of self-administration there have been advances in patient training beyond placebo injections into an orange or into themselves. Innovation has brought about simulation of needle force, punctuation force and even the sensation of a real injection to help the patient become familiar with what a real injection is like before actually having to perform a real injection. This is beneficial to both the user and pharmaceutical company by empowering the patient be familiar with a device and the correct technique before using a syringe loaded with the actual costly formulation that may provide relief for their affliction.

With the increase in HCPs providing patients and caregivers with in-office injection training – and payers looking for outcomes – the pharmaceutical industry is evolving and seeking improvements in adherence and market differentiation by incorporating pre-filled syringe device trainers and other patient onboarding products into launch strategies. Pharmaceutical companies are utilizing device training products and patient onboarding specialized companies such as Noble – which are dedicated to human factors and clinical research – to work with and complement commercial teams' launch strategy. The end result is the creation of a full-service launch ready platform incorporating the combination drug platform and also a training device that exactly emulates the puncture and needle simulation forces as well as safety mechanisms involved to help patients gain confidence, decrease anxiety and ultimately be more adherent. As a part of these platforms to help increase patient outcomes and market differentiation there are mechanical and connected smart devices, patient-friendly instructions for use and quick tip, travels materials and more.

Materials Selection Part II

1:45

Lubricious Coatings for Particle Reduction in Pre-Filled Syringes for Therapeutic Biologics**Susan M. Dounce, Ph.D., Sr. Manager, Datwyler**

For biologics, the potential for the generation of proteinaceous particles in pre-filled syringes is a concern. Under certain circumstances, therapeutic proteins can interact with syringe components, in particular, the silicone oil that is typically used as a lubricant on both the barrel and plunger. The potential risk for protein aggregates to elicit adverse patient reactions has triggered a shift in regulatory requirements related to particles in primary containers. While historically the regulatory focus has been on larger particles which could cause capillary occlusion, new additional scrutiny aims to reduce the immunogenicity risk associated with protein aggregates. Here we discuss strategies for material selection to reduce the risk for particles in prefilled syringes for therapeutic biologics.

2:30

Afternoon coffee & networking break

2:55

Butyl Rubber for Pharmaceutical Packaging**Dr. Dana Adkinson, Arlanxeo**

The demands by the medical and pharmaceutical sectors on elastomers, their compounds and vulcanizates, are extremely high. Manufactured to stringent requirements, pharmaceutical stoppers and plungers, which are used to preserve drugs and medications, often come into direct contact with pharmaceutical products, either dissolved or in other forms. For pharmaceutical packaging the elastomer must have good impermeability, low levels of additives, excellent resistance to aging and the ability to be vulcanized using low levels of curatives. In addition, the elastomer used must comply with existing standards and regulations relating to the contact of rubber articles with pharmaceuticals. Halogenated butyl rubber (both bromobutyl and chlorobutyl rubber) fulfills these requirements and these elastomers are widely used in pharmaceutical rubber products, such as closures for infusion containers and blood collection tubes as well as in plungers for pre-filled syringes.

An overview of halogenated butyl rubber pharmaceutical formulations, key vulcanizate properties and phar-

3:40

CASE STUDY

Advances in Deterministic Parenteral Container Closure Integrity**Ms. Chandra Minns, R & D Manager, pti, Packaging Technologies and Inspection**

This presentation outlines the challenges facing parenteral Container Closure Integrity (CCI) and recent developments in specific methods listed in USP 1207. The presentation will specifically explain the theory and application of the MicroCurrent HVLD, a next generation technology aimed at inspecting the integrity of a wide class of parenteral products and container formats. High voltage leak detection is included in USP 1207 as a deterministic test methodology. The presentation will cover practical implementations, and present hard data in the use of High Voltage Leak Detection for parenteral products.

The MicroCurrent HVLD technology uses unique voltage and current characteristics to inspect parenteral products with a wide range of product characteristics. Traditional HVLD has proven to be an effective solution for parenteral class products, with the MicroCurrent HVLD increasing the range of liquids that can be tested, and improving the overall safety of the high voltage solution. The nature of MicroCurrent HVLD allows for testing packages containing liquids with extremely low conductivity, such as sterile water (WFI). MicroCurrent HVLD reduces voltage exposure of the product to less than 5% when testing with comparable HVLD solutions, greatly reducing the voltage exposure to the product and environment.

The objective of the presentation is to provide attendees with an in-depth overview of the deterministic parenteral CCI methods as well as provide statistical test result data on BFS, syringes and vials. The study will draw on some comparisons between the new MicroCurrent HVLD technology compared with conventional HVLD methods. Attendees will learn the different aspects of different High Voltage applications for both traditional and MicroCurrent technologies.

4:20

Close of Program

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