PharmaED RESOURCES, Inc.

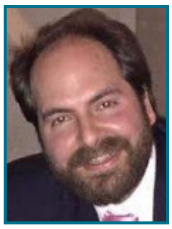
2017 Pre-Filled Syringes Forum:

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

December 7–8, 2017—West Coast, La Jolla, CA

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

Tiffany K. McIntire
Sr. Human Factors Engineer, Eli Lilly

Padam Sharma
Subject Matter Expert, Sterile Product, Injectables, Teva Pharmaceuticals (Allergan)

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:

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Thursday, December 7, 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

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 expectation 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/OCP
- 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.

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

A Cautionary Tale About Injection Pen Human Factors Research Gone Bad

CASE STUDY

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

10:00 *Mid-Morning Coffee & Networking Break*

10:25

Revision of USP's General Chapter <381> Elastomeric Closures for Injections as it Relates to Pre-Filled Syringes.

Michael N. Eakins, Ph.D., Principal Consultant, Eakins & Associates

Primary packaging components for pre-filled syringes includes elastomers as well as both glass and plastic barrels. The USP published a major revision to General Chapter <381> in the Pharmacopeial Forum 43(3) on May 1, 2017 and is in the process of evaluating the comments received. Major changes have been made to chapter <381> in that functionality of elastomers has been moved to its own chapter <382>. The revised chapter <381> now titled "Elastomeric Components Used in Injectable Pharmaceutical Packaging/Delivery Systems", emphasizes the baseline requirements for the selection of thermoset and thermoplastic elastomeric components, expands the scope to include all elastomeric components used in an injection packaging system, and assesses extractable elements using modern methods. A new informational chapter <1381> "Elastomeric Evaluation of Elastomeric Components Used in Pharmaceutical Packaging/Delivery Systems" by describing elastomeric components and their materials of construction, providing a high-level introduction to elastomer chemistry and manufacturing technology, and explaining basic functional characteristics of components. Functionality tests now appear in chapter <382> "Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging/Delivery Systems" and this chapter is supported by a new informational chapter, <1382> "Elas-

tomeric Evaluation of Elastomeric Components Used in Pharmaceutical Packaging/Delivery Systems". These new chapters will be discussed in general and how they relate to components for pre-filled syringes.

11:10 **Enabling a Patient-Friendly Design: Robust Design Control for Connectivity of a Co-Packaged Combination Product**

CASE STUDY

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 require 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.

12:00 ***Complimentary Lunch & Networking Hour***

1:00 **Sterile Manufacturing of Injectables**

Padam Sharma, Sterile Manuf. & Dev, Injectable, Aseptic Processing, Fill-Finish, Combination Products, External manufacturing at CMOs, Teva Pharmaceuticals, (Allergan)

Sterile manufacturing of injectables, especially prefilled syringes, is a complicated process. The compounding and packaging processes are carried out in Grade A environment while providing sterility assurance. Injectables are produced as 'ready-to-use' and lyophilized products. Ready to use products are stable in liquid dosage form. Lyophilization process is used for unstable products such as proteins and biologics to increase shelf life and expiry periods. Sterile manufacturing of these products will be discussed.

Technology Spotlight—Considerations for Patient-Centric Designs

1:45 **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 will focus on the sources for user-relevant requirements for the design and development of combinations products.

2:30 **Identifying and Managing Use-Related Risk Through Human Factors**

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

When asked a question a Human Factors (HF) engineer will often tell you "it depends on your risk assessment." With a heavy reliance on industry guidance (e.g. IEC62366, ISO14971, HE75), this presentation will guide you through the process of how to begin forming that risk assessment. Often when people think about HF, they think about formative and Summative testing. While this is a way to evaluate the effectiveness of some of your design controls, that alone may not lead to safe design. Involving HF earlier in your process can reduce the use errors observed later in the product timeline, thus reducing interruptions and associated cost.

Safety Evaluation of Pre-Filled Syringes—Special In-Depth Coverage

3:15 **Analytical Challenges and State of the Art Solutions Related to Chemical Safety Assessment of Pre-Filled Syringes**

CASE STUDY

Gyorgy Vas, Ph. D., Business-Technical Scientific Liaison, Intertek Pharmaceutical Services, (Contributing Authors: Louis Fleck, Jiun-Tang Huang)

Pre-Filled Syringes (PFS), are finished pharmaceutical products, what are packaged into the special delivery device, over a period of the intended shelf-life. Both the formulation and the route of delivery present relatively high risk for toxicological risk assessment. To have the safety risk assessment performed properly chemical testing needs to be executed appropriately, based on

high level analytical and quality standards. PFS finished products are often formulated and delivered in a complex matrix, as well as the low-level impurities leaching out from the delivery system adding an extra layer of complexity of the testing. To use complex and sophisticated analytical instrumentation been always required for providing reliable data for chemical safety assessment. New developments from the analytical instrument manufacturers re-shaped the testing industry. High performance extraction methods combined with various MS/MS and high resolution accurate mass (HRAM) detection, providing testing solutions for low level analytes in highly complex matrices, such as PFS finished products. This presentation will focus on a few case studies where high performance complex instrumentation was used on a routine basis for safety evaluation of PFS products.

4:00 **Challenges in Extractable and Leachable Studies of Pre-Filled Syringes**

CASE STUDY

Dujuan Lu, Ph.D, Technical Manager-Life Science Extractable and Leachable Testing, SGS North America Inc.

Pre-filled syringes (PFS) are increasingly becoming a container of choice for storing and administering pharmaceutical products. PFS components and residues from processing tools may leach organic and inorganic chemicals into formulated drugs, as extractable and leachable compounds. As part of safety risk assessment, it is very important to identify and quantify those extractables and leachables as they may pose safety risks to patients and/or change the efficacy of the medical products.

This presentation will focus on a case study regarding the extractable and leachable testing of PFS for a drug formulation containing high content of castor oil. The choice of the extraction solvent systems and study design to bracket and mimic hydrophobicity and administration of drug formulation will be discussed. In order to obtain a comprehensive extractable profile, multiple analytical techniques were used to identify and quantify the extractables, including Headspace (HS)-GC-MS/FID analysis for volatile organic compounds, GC-MS/FID analysis for semi-volatile organic compounds, LC-MS/UV analysis for non-volatile organic compounds, and ICP-OES analysis for trace elements. This presentation will show that internal database and High Resolution Accurate Mass (HRAM) data facilitate confident compound identification and unknown compound structure elucidation. Analytical challenges associated with the drug formulation containing high amount of castor oil during the leachable testing will also be discussed.

Panel Discussion

4:40 **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:

Edmond Israelski, Consultant, Retired Director Human Factors, AbbVie

Padam Sharma, Teva Pharmaceuticals

Nicholas Zampa, Pfizer

5:20 ***Close of Program Day One***

Friday, December 8, 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 **Challenges Associated with PFS Combination Product Development for Ophthalmic Applications**

CASE STUDY

Mayumi Bowen, Senior Engineer, Pharmaceutical Processing Technology Development, Genentech, Inc.

There are stringent Health Authority guidance and ISO requirements for ophthalmic applications to prevent infection by eliminating pathogenic micro-organisms, considering eye safety, which are challenges to development of ophthalmic PFS combination products. This presentation will address guidance & requirements pertaining to particulate, endotoxin, silicone oil leachates, and external surface sterilization for ocular applications. In addition, points to consider, strategies, and case studies regarding material selections (e.g. PFS container closure, label, and sterile barrier system, etc) and sterilization process development to meet the stringent guidance and requirements.

8:45 **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 systems. This presentation will cover the latest developments of large volume autoinjectors, wearable devices as well as the completely new field of connected, smart devices.

9:30 ***Mid-Morning Coffee & Networking Break***

9:55 **Challenges and Opportunities for Development of Stability Program for Combination Products**

Alireza (Alie) Jahangir, Ph.D, Sr. Manager Combination Product Device Quality, Janssen Pharmaceuticals

Combination products are unique therapeutics that combine two or more regulated constituent parts (i.e. drugs, devices and/or biological products), leading to products that provide ease of use, safer and more effective. While the combination products have been developed and commercialized as a result of unprecedented collaboration between pharma and device industries to address patients' unmet therapeutic needs, they also have presented new regulatory, quality and development challenges. Unlike the stability program of pharmaceutical products, the combination product shelf life is not only determined by the effectiveness of a particular drug formulation, but also by device functionality as well as the sterile barrier system materials integrity during the product's entire supply chain from packaging to sterilization, transportation and storage. From a combination product perspective, while the individual shelf life data for each of the above-mentioned entities are critical, the complete stability testing plan should also include monitoring of the specific Stability Indicating Attributes/Parameters that demonstrate the interactions among these various constituent parts. Furthermore, in addition to following different international standards and guidelines (i.e. ICH, WHO, ASTM), governing the stability testing requirements for drugs, devices and/or their packaging systems, the manufacturers should also be aware of differing expectations by two review centers within FDA (i.e. CDER and CDRH) for approval of a drug/device combination product. Accordingly, by using case studies and industry best practices, this presentation will introduce a new end-to-end stability testing paradigm for different classes of combination products based on robust scientific, risk-based, holistic and proactive approach.

10:40 **Challenges of the Implementation for a "Standard Drug Container/Syringe" into a Modern Auto Injector**

Bruno Reuter, Executive Director, Scandinavian Health Ltd.

Modern types of auto injectors still using standard types of drug container as e.g. standard 1.0mL long and 2.25mL – staked needle syringes. The complexity of such a device and the tight specification in terms of injection time, injectable volume accuracy and other specified items leads at the end to a specific requirement profile for such a drug container which is not implemented in the pharmaceutical industry so far. The challenges for all parties; pharmaceutical end user, device manufacturer as well as primary container manufacturer, are not aligned so far and in most cases, the common understanding is still missing.

The presentation highlights some of these "imperfections" between device and drug container, at least no part of this "manufacturing triangle" can solve it alone, a common understanding and solution is necessary for an optimal solution at all.

Materials Selection in PFS for Biologics

11:20 **Testing and characterization needs for combination products**

Robert Schultheis, President, ZebraSci, Inc

Complete characterization of primary packaging, formulation, and device is essential to launching combination products in a timely fashion. This presentation will show some of the variability that ZebraSci Labs has encountered in in root cause investigations and in combination product development programs.

12:00 *Complimentary Lunch & Networking Hour*

1:05 **Filling of High Concentration Monoclonal Antibody Formulations: Challenges in Filling Accuracy**

Wendy Shieu, Engineer II, Genentech, Inc., Pharmaceutical Processing and Technology Development

Filling of high-concentration/viscosity monoclonal antibody (mAb) formulations into vials or syringes by peristaltic pumps is an industrial standard. Control of the peristaltic pump on fill weight/volume accuracy/precision over time, however, has not been fully disclosed in the literature. This study systematically evaluated the impact of a broad range of system/pump parameters, from tubing set up to pump parameter settings to the filling nozzle, on filling precision using a bench-top system with fill weight readings from a high-precision balance. A low fill volume of 0.3 mL was targeted to fill liquids of various viscosities (including a high-concentration mAb formulation). Fill weight precision was reported via percent of fill weight data points (at least 100 consecutive points) falling within 3% of the target fill weight (e.g., within 0.009 g for a 0.3 g target fill weight). Experimental results suggested that the 3% precision target is challenging for filling high-viscosity liquids due to run-to-run and day-to-day variability. More importantly, none of the system/pump parameters seemed to directly correlate with fill weight precision.

1:50 **Considerations for Selecting Drug Delivery Systems**

Justyna Dudaronek, PhD, 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.

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

2:30

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.

Materials Selection Part II

3:15

CASE STUDY

COP Technical Data Update

Toshiro Katayama, Product 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 bene ts for prefilled 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**

4:00

Close of Program

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