

Inhalation Drug Delivery Systems 2019

Ensuring Quality, Safety and Regulatory Compliance
for Inhalation Drug Delivery Systems
May 28–29, 2019, Boston, MA

Featuring Lessons Learned and Case Studies From Industry Experts:



George Cusatis
Merck



Marco Laackman
Harro Höfliger



Badre Hammond
Aptar



Vibha Puri
Celgene



Hugh Smyth
University of Texas



Michael Eakins
Eakins & Associates



Dino J. Farina
Proveris Scientific Corporation



Anselm Ebert
H&T Presspart



Pavan Muttil
University of New Mexico



Daniel Norwood
Feinberg, Norwood and Assoc.



Meredith Earl
Liquidia Technologies



Larry Brown
Noveome



Allen Kesselring
EKG Labs



Dries Gardoen
Nelson Labs



Anup Paul
Stress Engineering Services



Gyorgy Vas
Intertek



Julian Stauffer
PTI

And Comprehensive Coverage On:

- Regulatory Compliance Issues for Inhalation Therapies
- Combination Product Design
- New Strategies for Showing the Bioequivalence of Inhalation Drugs
- Achieving an Inhaled Insulin Product
- Powder Dosing and DPI Manufacturing Technologies
- Developing a Generic Inhaled Product
- Sterilization Issues Surrounding Inhalation Therapies
- Extractables and Leachables Testing
- Nebulizers
- Alternative Therapeutic Fields: Inhaled Antibiotics
- Non-invasive, Targeted Intranasal ST266 Delivery for Optic Nerve Disease and Trauma
- Future Directions in Inhalation and Respiratory Drug Delivery Research
- Novel Technologies for Pulmonary and Nasal Delivery
- The Challenges of Developing Inhalation Devices
- Applying QbD Principles to Inhalation Therapies
- Improving Patient Adherence With Product Design
- Establishing Clear Relationships Between in Vitro and in Vivo Data
- Delivery of Inhaled Drug Products Using PRINT Technology

Featuring Representation From:



Tuesday, May 28, 2019

7:30 *Complimentary Breakfast*

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

Regulatory Considerations

8:30 **Demystifying the Regulatory Environment for Drug-Device Combination Products**



George Cusatis, Associate Director, Device & Digital Health, Merck

Over the past several years, combination products (which include pre-filled syringes) have become more of a household name both from an Industry and Health Authority perspective. It is only fitting that as the number of combination products available on the market continues to increase from previous years, so does the available guidance and scrutiny from regulators around the world. Legislation such as the 21st Century Cures Act, and the European Medical Device Regulation (MDR), has shed light on the direction that the regulation of combination products is heading. In this presentation, we will take a look at the evolving global regulatory landscape for combination products, best practices for regulatory filings, identification of regulatory opportunities and challenges, and future regulatory considerations for combination products as we move forward.

9:15 **Best Practices for Establishing and Controlling a Robust Method for Inhalation Drug Product *in vitro* Testing**



Dino J. Farina — Founder and CEO, Proveris Scientific Corporation

Current FDA recommended guidelines for release testing of inhalation drug products include general descriptions for performing delivered dose uniformity, aerodynamic particle size distribution, and spray pattern tests as key indicators of inhaler product quality. However, the actual performance of inhaler products is highly dependent on patient usage (e.g. shaking duration, shake-to-fire interval, actuation, hold down time, etc.), particularly for suspension formulations. A recent study reported that the use of improper shaking and shake-to-fire intervals can result in 75% to 320% of delivered dose label claim for some popular inhalers – indicating significant over- and under-dosing of people who may improperly use these products. Given these known sensitivities, controlling the shaking and actuation processes during testing is the only way to measure the true variations in the drug product's performance. Moreover, firing down in between testing represents 83 to 95% of the actuations for each device and introduces the highest source of error in through life testing if not performed in a consistent and reliable manner.

The presentation will focus on best practices for establishing human realistic shaking and actuation parameters, and how to use these parameters with controlled automated actuation systems that support robust testing of inhaler products, including the critical fire down process. In addition, time sequenced actuation results will be presented that indicate

inhaler valve performance and how these dynamic measurements can be used for troubleshooting out-of-specification results during inhaler manufacturing and quality control.

10:00 *Networking Break*

10:30 **USP Chapters Addressing Key Quality Attributes for Inhalation Drug Products**



Michael Eakins, Principal, Eakins & Associates

Inhalation drug products deliver a drug substance into the lungs by oral inhalation in various forms including inhalation, powders, sprays, solution, and suspension dosage forms. Several USP chapters directly address various key quality attributes for the delivery of inhalation drug products including *Inhalation and Nasal Drug Products — General Information and Product Quality Tests* <5>, *Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests* <601>, *Products for Nebulization — Characterization Tests* <1601>, *Spacers and Valved Holding Chambers Used With Inhalation Aerosols—Characterization Tests* <1602> and *Pharmaceutical Dosage Forms* <1151>.

The required physicochemical tests for inhalation and nasal drug products are listed and described in <5> while methods for major performance measures relating to dose delivery to the patient, such as delivered-dose uniformity and particle size measurements are provided in <601>. A draft revision of <601> was published in the Pharmacopeial Forum 44(5) September 2018. A revised version of General Information chapter <1601> became official June 2018 which provides guidance on the drug substance delivery rate, total drug substance delivered and the aerodynamic assessment of nebulized aerosols. A new chapter <1602> became official April 2017 and defines potential standardized methods for characterizing the *in vitro* performance of a given metered dose inhaler (MDI) drug product with a specific spacer and valve holding chambers. The presentation will provide an overview of key points in these chapters.

Other key quality attributes for inhalation drug products are addressed in chapters devoted to plastic and elastomeric packaging materials that are used to construct inhalation delivery systems and also extractables and leachables from packaging materials. The chapter *Elastomeric Closures for Injections* <381> is undergoing a major revision and a proposed revision was published in the Pharmacopeial Forum 43(3) May 2017 that added a new General Information chapter <1381> and also moved the functional requirements into a new chapter <382> with an accompanying General Information chapter <1382>. The presentation will review the proposed changes and how these changes will affect elastomeric components used in inhalation delivery systems. Chapter <1664> *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* became official in 2015 and included a subpart <1664.1> *Orally Inhaled and Nasal Drug Products*.

11:15 Inhalation Regulatory Panel

- George Cusatis, Associate Director, Device & Digital Health, Merck
- Michael Eakins, Principal, Eakins & Associates
- Dino J. Farina, Founder and CEO, Proveris Scientific Corporation

12:00 Complimentary Lunch

Challenges for Dry Powder Inhalers

1:00 Delivery Challenges for Lung Infections: Inhaling Drugs and Unveiling Bugs



Hugh Smyth, Professor of Pharmaceutics, University of Texas

Inhaled antimicrobials have a long history of success in the clinic but several formidable challenges to developing these products exist. This presentation will address these challenges and opportunities by reviewing past successes and failures while discussion of newer therapies and delivery strategies underdevelopment.

CASE STUDY

1:40 Looking Through Magnifying Lens: Investigating API, Excipient, and Process Effects on Performance of Dry Powder Inhaler Formulations



Vibha Puri, Celgene

Carrier-based dry powder inhaler formulations have been challenged with issues of low drug delivery and inconsistent aerosolization performance. This presentation will discuss examples of better understanding of formulation and process variables studied using advanced characterization tools.

2:20 Afternoon Break

2:45 In Silico Methods—Computational Modeling and Simulations for Combination Product Development



Anup Paul, Ph.D., P.E., Senior Associate, Stress Engineering Services, Inc.

Computational Modeling and Simulations (CM&S), i.e. *in silico* methods, can be used throughout the device lifecycle supporting discovery, ideation, product design, reliability assessment, manufacturing process and failure investigation activities. In this presentation, we discuss the evaluation of a Dry Powder Inhaler (DPI) product using CM&S methods. Computational modeling can be applied to assess the capability of the DPI design to maximize the drug dose per inhalation and minimize the dose-to-dose variations. Additional simulations can evaluate the reliability of mechanical systems like dose counters and also manufacturing processes. The design can be evaluated for the range of design and use variables, thus ensuring a robust design even before prototypes are generated for testing.

As the reliance on computational models increases there is a need to ensure that the models represent a *credible* approximation of reality. *In silico* data obtained from cred-

ible models can be leveraged for regulatory submissions. The recently published American Society of Mechanical Engineers (ASME) V&V 40 standard provides procedures to standardize the *verification, validation and uncertainty quantification* (VVUQ) necessary to demonstrate the credibility of computational models for medical devices. Data obtained from physical testing is necessary to define adequate inputs to the model and to validate the outputs.

This presentation will use case studies to focus on the following points:

- Application of *in silico* methods for development of combination products for inhaled therapies.
- Leveraging test methods to obtain data for model input and verification/validation of outputs.
- Overview of the ASME V&V 40 standard for computational modeling of medical devices.
- Leveraging *in silico* data for regulatory submissions.

3:25 Delivery of Inhaled Drug Products Using PRINT Technology



Meredith Earl, Principal Scientist, Liquidia Technologies, Inc.

Authorship: Meredith Earl, Stephanie Anderson, Brian Farrer, Robert Roscigno, Toby Vaughn, Ben Maynor

CASE STUDY

The PRINT® technology is a particle engineering platform that enables precise control of particle size and shape for a wide range of particle compositions. We believe this control can result in improved drug delivery. Liquidia has leveraged the PRINT technology to design particles for inhaled products. Liquidia's lead product, LIQ861, is a dry powder formulation of Trepstinil which leverages the benefits of local delivery in the lung for the treatment of pulmonary arterial hypertension. LIQ861 is specifically designed to maximize the therapeutic benefits of Trepstinil in a convenient and easy to use dry powder inhaler. A summary of the preclinical toxicology and results from Liquidia's Phase 1 safety, tolerability, and PK single ascending dose study in healthy volunteer subjects will be presented.

4:05 Non-invasive, Targeted Intranasal ST266 Delivery for Optic Nerve Disease and Trauma



Larry R. Brown, Sc.D., Executive Vice President, Chief Scientific Officer, Noveome Biotherapeutics, Inc.

Optic neuritis (ON) is demyelinating inflammation of the optic nerve that often occurs in multiple sclerosis (MS). ST266 is a proprietary secreted product from Amnion-derived Multipotent Progenitor cells derived from full-term C-sectioned placentas. Animal models have shown that ST266 blocks inflammation, reduces vascular permeability and is neuroprotective. We measured brain and optic nerve deposition of radiolabeled ST266 after targeted intranasal delivery in rats and cynomolgus monkeys. Radiolabeled ST266 accumulated throughout the brain with the highest concentrations found in the optic nerves. Experimental autoimmune encephalomyelitis (EAE) MS mice were intranasally treated

CASE STUDY

with 6µL of ST266 after onset of ON. Intranasal ST266 significantly increased visual acuity, preserved retinal ganglion cells and significantly reduced optic nerve inflammation and demyelination, resulting in clear therapeutic effects in the EAE model. Similar results were observed in an acute trauma, optic nerve crush model. These studies demonstrated the potential to use the intranasal delivery route to access the brain and successfully treat the optic nerve with a complex mixture of large molecular weight biomolecules. The ability to bypass the blood-brain barrier non-invasively and potentially treat other central nervous system tissues has broad implications for suppressing inflammation in other neurodegenerative diseases. A phase 1 trial of ST266 delivered by the novel route of administration is planned in 2019.

4:45 *End of Day One*

Wednesday, May 29, 2019

7:30 *Complimentary Breakfast*

8:15 *Chairperson's Remarks*

Extractables & Leachables Considerations

8:30 **Commentary on the Past Twelve Years of Implementing the PQRI Leachables and Extractables Recommendations for OINDP**

Daniel Norwood, Senior Consultant, Feinberg, Norwood and Assoc.

- What was done right.
- What could be improved.
- Why things were done the way they were.
- What are the gaps?

The Product Quality Research Institute (PQRI) recommendation document entitled "SAFETY THRESHOLDS AND BEST PRACTICES FOR EXTRACTABLES AND LEACHABLES IN ORALLY INHALED AND NASAL DRUG PRODUCTS" was submitted to FDA on 8 September 2006. Since that time, these recommendations have been widely implemented in the pharmaceutical industry and endorsed publicly by regulatory authorities around the world. This presentation will give an "insider's look" at the process of developing the recommendations, as well as discuss their implementation. It will also attempt to present a balanced perspective on what was done right, what could be improved, and where the gaps are in these recommendations. Efforts to fill the gaps and improve the recommendations will also be discussed, along with the pivotal role that USP has played since 2006.

9:10 **Extractables & Leachables for Inhalation Products – From Basic Concepts to Study Designs**

Dries Cardoen, Scientific Director at Nelson Labs Europe

The level of concern and the need for Extractables and Leachables testing required by health authorities, is associated with both the risk of interaction between the

Drug Product and the container/closure system and with the route of administration (USP 1664). To further complicate the picture, regulatory concern regarding extractables and leachables in OINDP's is directly related to the particular type of OINDP, such as Metered Dose Inhalers (MDI), Dry Powder Inhalers (DPI), Inhalation solutions and Nasal Sprays (as per USP 1664.1). This chapter includes recommended exposure thresholds (SCT, QT) above which individual organic leachables in an OINDP must be qualified and/or evaluated for safety concern. These "safety thresholds" are then linked to the recommended Analytical Evaluation Threshold (AET) which basically answers the question of "How low do you go?"

A tailor made approach in designing E&L studies for OINDPs, together with best practices and the threshold approach will be explained through case studies.

9:50 *Morning Break*

10:20 **Hitting the Limit: Challenges and Considerations Behind Successful Extractable and Leachable Method Design**



Allen Kesselring, Director of Science & Operations and Founding Member, EKG Life Science Solutions

Beginning with the origins of modern Extractable/Leachable studies, the risk of inhalation products exposing patients to deleterious materials is widely recognized as significant. As both inhalation packaging/container size and dosing quantities can vary significantly, the development of appropriate extractable and leachable methodologies can vary from the near routine, to situations that are near impossible. This presentation will cover several topics including limits of analysis, levels of interest, proper design of experiments, sample preparation concerns and the need for proper controls in the development of useful leachable analysis.

11:00 **The HFA Challenge: The canister role as an integral part of the pMDI drug delivery system**



Dr. Anselm Ebert (Ph.D. in Neuroscience) is now Director of the Business Development Department at H&T Presspart

The canister historically was a safe containment system for CFC + API, and the only difference from can to can was size: Taller, thinner, shorter, fatter, however 65 years on with the introduction of HFA and complex formulations, combinations the canister plays a significant role in the efficacious delivery of the drug to the patient. The relationship between propellant, drug and canister has significantly changed. Different technologies can be used to accommodate this relationship. A new plasma surface treatment for MDI canisters, presents its advantages compared to existing technologies.

11:40 **Extractables & Leachables Panel**

- Dries Cardoen, Nelson Labs Europe
- Allen Kesselring, EKG Life Sciences
- Daniel Norwood, Feinberg, Norwood and Assoc.
- Gyorgy Vas, Intertek

12:10 *Complimentary Lunch*

1:10

Decoding FDA's Recent Combination Drug Product Guidance: Applications to DPIs, pMDIs, and Nasal Sprays

Badre Hammond, Director, Aptar



This presentation will provide guidance on how the 2018 guidance affect future respiratory drug product submissions and an overview on Combination Products FDA guidance focusing on respiratory and nasal drug products, specifically DPIs, pMDIs, and Nasal Sprays. In addition, insights on optimal approaches to help secure approval in this changing and challenging regulatory landscape including EMA's strategy as they elevate their requirement in this space.

The second part of the talk will introduce a novel new technology using material science embedded in three phase polymers to create a fit for purpose integrated solution to improve stability and other environmental considerations.

Nasal Inhalation and Packaging Solutions

1:55

Medical Inhalation Packaging Solutions

Julian Stauffer, COO, PTI



Medical products are manufactured and packaged for sale around the world. These critical high risk products are subject to the most diverse climate conditions, whether it be extremely high air humidity or by contrast, extremely dry air. The air pressure at sea level is significantly lower than in the Rockies or in an airplane. The packaging for these medical products must ensure product consistency and potency from the Equator to the polar regions. This is not a problem for small tablets in blister packs but presents a bigger challenge for a two-component drug inhaler with a lot of headspace. Waldner was faced with a specific challenge from one of the world's largest pharmaceutical companies to produce a highly secure seal for surviving dynamic global environments, while also enabling an easy peel for people of lesser strength. This case study will discuss project application scope and inhalation product packaging solutions developed by Waldner that met the unique challenges of packaging this medical product.

This presentation will also review package integrity testing technologies for leak testing and non-destructive altitude testing.

2:40

Afternoon Break

2:55

Poor Translational Success of Inhalation Products: Different Mechanism of Preclinical Delivery Devices and Clinically Irrelevant Animal Models

Pavan Muttil, Associate Professor, College of Pharmacy, University of New Mexico



Significant progress has been made over the last half-century in delivering therapeutics by the pulmonary route. Inhaled therapeutics are commonly

administered to humans using metered dose inhalers, nebulizers, or dry powder inhalers, and each device requires a different formulation strategy for the therapeutic to be successfully delivered into the lung. Numerous pre-clinical studies, involving small and large animals, have evaluated aerosol drugs, vaccines, and immunotherapeutics that are delivered by the pulmonary route. These pre-clinical studies used different delivery devices including nose-only, whole-body, and intratracheal administration systems, each of which works with different aerosolization mechanisms. Unfortunately, these delivery platforms usually lead to variable drug deposition in the respiratory tract of animals. Further, the animal models used in these studies rarely represent the human lung anatomy and physiology.

What the attendees will learn from this talk:

1. Obstacles and variables that affect successful pulmonary delivery in animal models based on:
 - a. Type of delivery device,
 - b. Type of formulation, and
 - c. The animal model used.
2. Factors that could enhance the reproducible deposition of drugs in the respiratory tract of preclinical animal models.
3. Factors necessary for successful translation of studies performed in preclinical models to humans.

3:35

Analytical Evaluation of Inhalation Based Drug or Delivery Systems and Medical Devices

Gyorgy Vas, Business Technical Scientific Liaison, Intertek



Inhalation based delivery devices are complex systems, and they are delivering active pharmaceutical components or recreational substances (nicotine, cannabis), or as another function, support live functions (anesthetic instruments). As the use of these products, systems and devices are complex, the analytical testing can be extremely challenging. According to the FDA packaging guidance as well as USP <1664> general chapter, the inhalation administration route has the highest risk.

As the wide range of application requires different level and different intensity testing, different regulations, regulatory guidances and standards, could guide the testing (USP <1163> for inhalation drug products, ISO 18562 for inhalation based medical devices).

This presentation will focus on the analytical testing issues for different inhalation products from inhalation based medical devices through the very popular electronic nicotine delivery systems.

CASE STUDY

CASE STUDY

4:15

Powder Dosing and DPI Manufacturing Technologies



Marco Laackman, Division Leader, Harro Höfliger

Dry powder inhalers on the market distinguish significantly in terms of powder fill weight, container closure system and manufacturing technologies. Reservoir-based inhalers, typically containing 0.2 to 1.0 g of powder, pre-metered DPIs based on hard capsules, blister strips, cartridges or disks, containing 1 to 25 mg of powder per dose unit and cannot be filled by using the same equipment. Several methods are available for industrial filling and manufacturing of DPIs, and in the course of product development it is important to know, which dosing system will be most appropriate to fill the given device and formulation. The originators developed diverse dry powder inhalation technologies. This complexity will be discussed in respect to up-scaling requirements from lab testing to commercial scale manufacturing.

4:55

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