


# OPQR Testing & Research to Support Guidance Development of Inhalation Products


**Advancing Generic Drug Development 2024:  
Translating Science to Approval**

*Day 1, Session 3: Research to Support Guidance Development for Inhalation Drug Products*

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A close-up photograph of a hand holding a small, orange, translucent plastic pill container. The hand is tilted, and three white, oval-shaped pills are falling from the container into the palm of another hand. The background is blurred, focusing attention on the pills and the hands.

Everyone deserves  
confidence in their *next* dose  
of medicine.

**Pharmaceutical quality**  
assures the  
availability,  
safety,  
and efficacy  
of *every* dose.

# Learning Objectives



- Be informed on FDA's laboratory support on inhalation drug assessment.
- Understand the research efforts conducted at FDA lab to support guidance development.
- List newly recommended in vitro studies as options to establish bioequivalence (BE) for inhalation products.

# OPQR Labs



Center for Drug Evaluation and Research (CDER)

– Office of Pharmaceutical Quality (OPQ)

• Office of Pharmaceutical Quality Research (OPQR)

Division of Pharmaceutical Quality  
Research II (DPQR II)

- Saint Louis, MO
- 1 of the 6 divisions under OPQR



# Inhalation Lab Capability



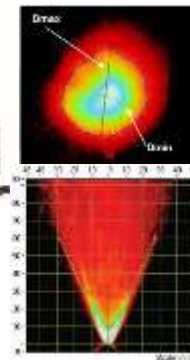
Delivery Dose Uniformity (DDU)



Aerodynamic Particle Size Distribution (APSD)



Spray Pattern & Plume Geometry



Laser Diffraction



Microscopy (MDRS, XRM, SEM, AFM)



Dissolution

# OPQR Inhalation Team



- Provide product testing and method validation program to support NDA/ANDA reviews and other regulatory actions.
- Evaluate emerging technologies and develop new methods to
  - Characterize inhalation product performance
  - Establish better in vivo in vitro correlation

# Product Specific Guidance (PSG)



## Alternative Bioequivalent (BE) Approaches

- Realistic APSD
- Laser Diffraction
- Particle morphology
- Evaporation rate and velocity profile
- Clinically relevant dissolution

The slide features decorative geometric patterns in the corners. The top-left corner has a blue and white triangular pattern. The bottom-left corner has a blue and white triangular pattern. The bottom-right corner has an orange and white triangular pattern.

# Realistic Aerodynamic Particle Size Distribution (APSD)



# Bio-Relevant Mouth-Throat Models



## USP Throat



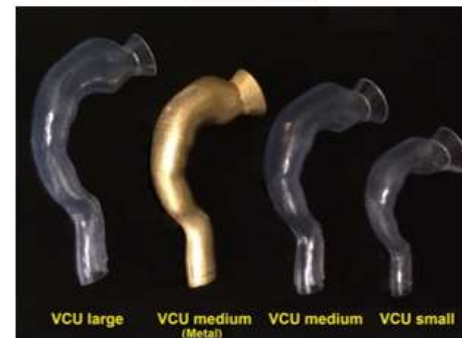
## Alberta Idealised Throat (AIT)

Commercial product



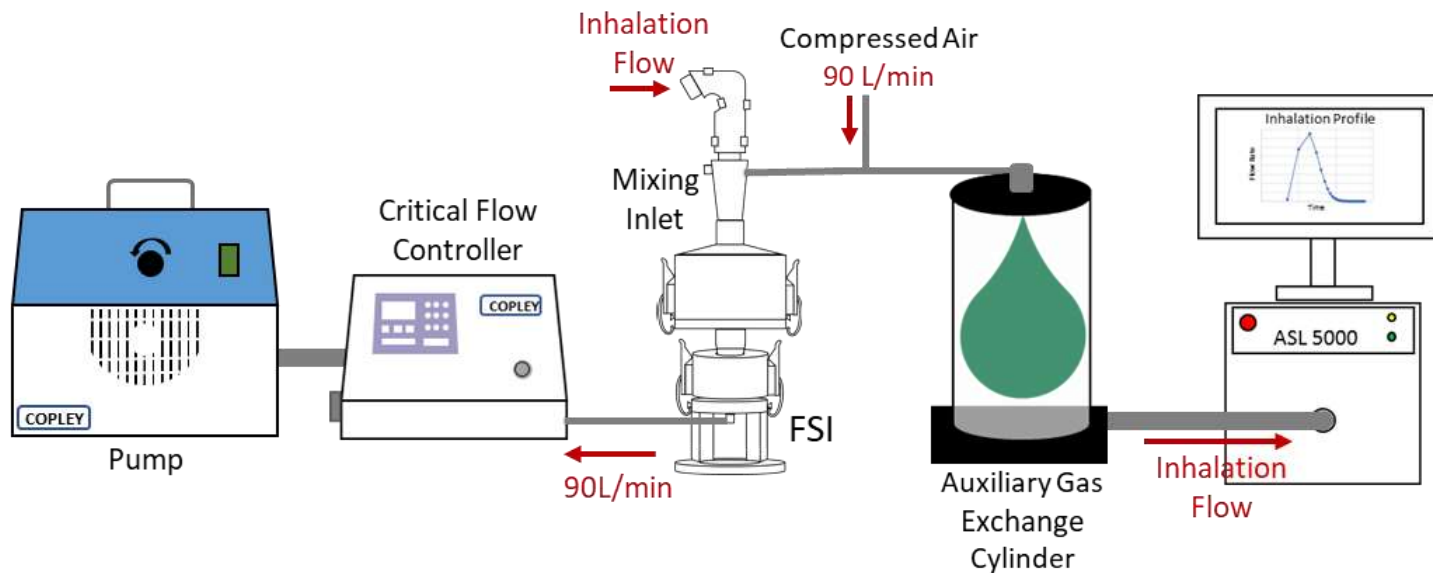
## Virginia Commonwealth University (VCU) models

3D printed



Reference:  
[www.rddonline.com/resources/tools/models.php](http://www.rddonline.com/resources/tools/models.php)

# Realistic Breath Simulation

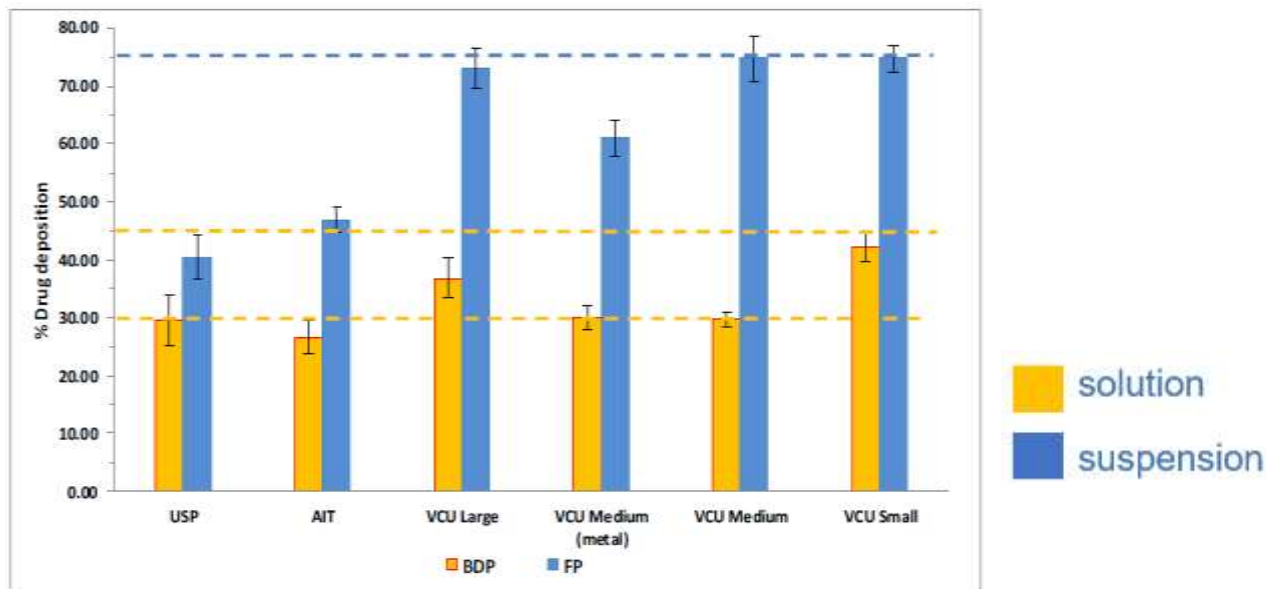


Schematic of realistic breath simulation experimental setup for DPI evaluation

# Bio-Relevant Mouth-Throat Models



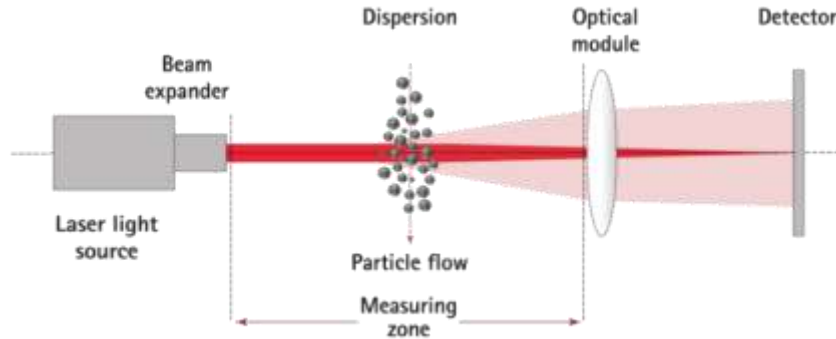
MT deposition (% emitted dose)



A. Kaviratna, G. Tian, X. Liu, R. Delvadia, S. Lee, C. Guo, Evaluation of Bio-Relevant Mouth-Throat Models for Characterization of Metered Dose Inhalers, *AAPS PharmSciTech*, 2019.

# **Laser Diffraction as an Alternative / Orthogonal APSD methods**

# Laser Diffraction



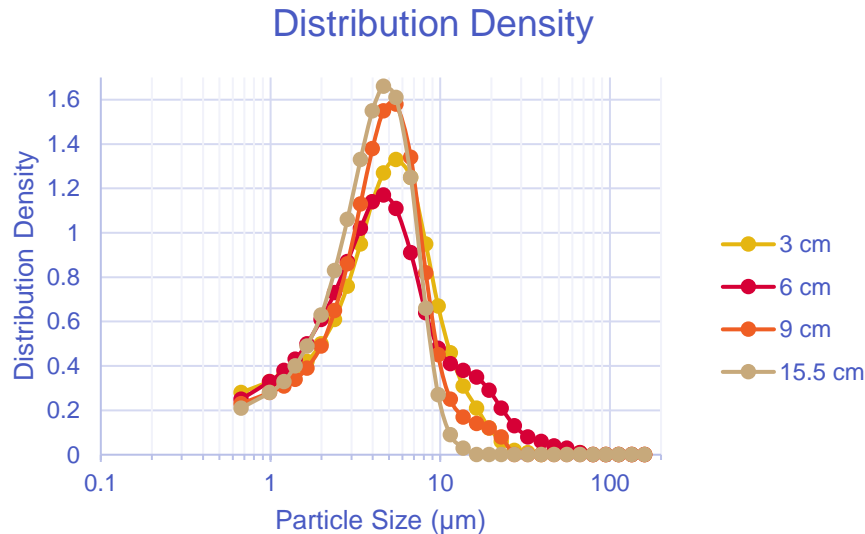
- Pros:
  - Rapid Measurements
- Cons:
  - Measures volume-based PSD, not Aerodynamic PSD
  - Not able to differentiate APIs and excipients

# Example for Supporting PSG



## Soft Mist Inhaler

### Spiriva Respimat

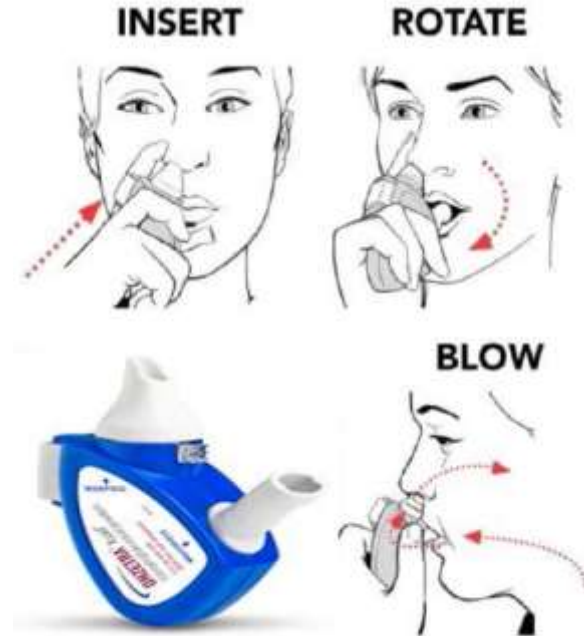
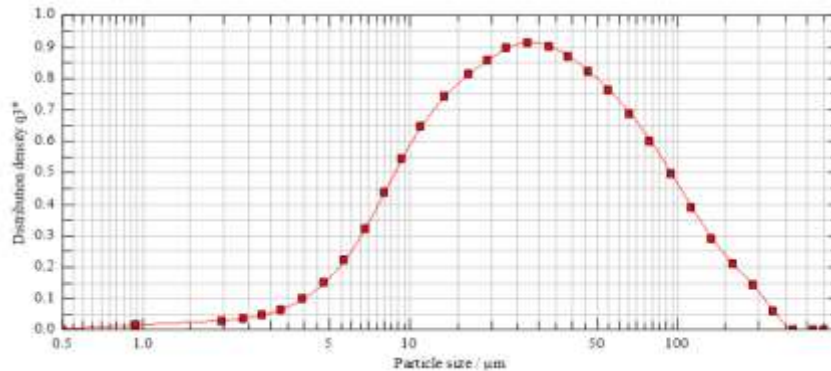


# Example for Supporting PSG



## Breath-Actuated Nasal Powder

➤ Onzetra Xsail

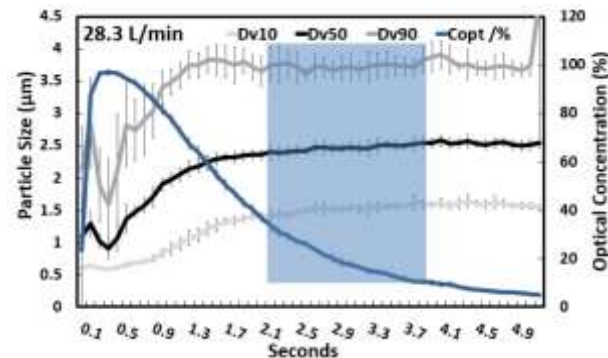
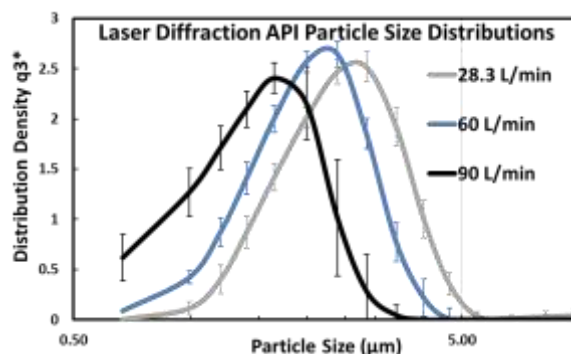
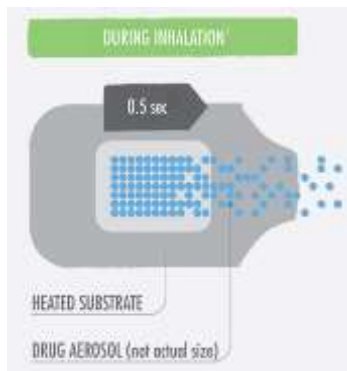


# Example for Supporting PSG



## Breath-Actuated Thermally-Generated Inhalation Powder

### ➤ Adasuve (Loxapine) Inhalation Powder



### **Laser Diffraction was not listed as an alternative method for APSD**

- Limitations in method due to high concentration of API particles

Elizabeth Bielski, Nathan Reed. "Loxapine Inhalation Powder: OTR Research Conducted to Inform the PSG Recommendations" SBIA 2023, Day 1, Session 2.

Nathan Reed et al "Characterizing Adasuve® (Loxapine, 10 mg) Inhalation Powder Particle Size Distribution Using Laser Diffraction". RDD 2024



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# Morphologically-Directed Raman Microscopy (MDRS)

# Why MDRS



Challenges for characterizing API particle size distribution in inhalation drug products:

- API and excipient particles coexist in the formulation
- More than one APIs in the formulation
- API may have more than one polymorphic form

# MDRS

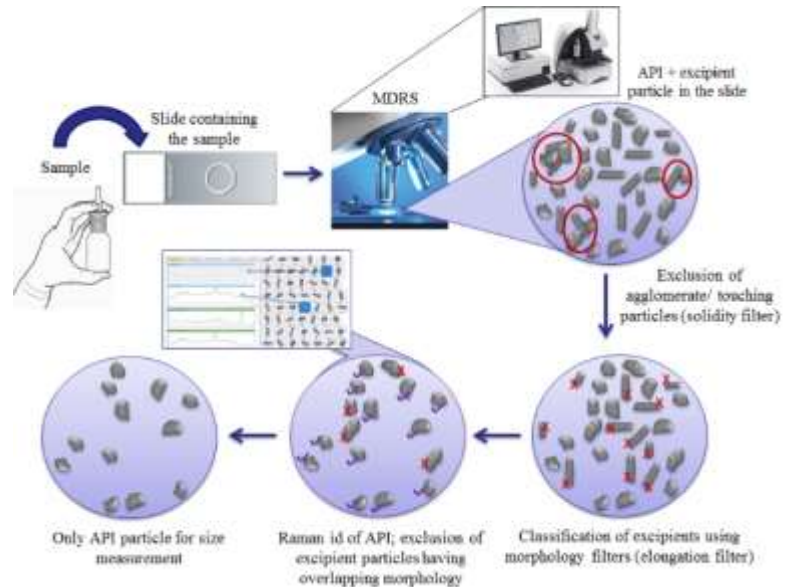
## A Raman microscopy system designed for particle sizing characterization

### Morphology Screening

- Capture particle image using digital microscope.
- Apply morphology filters to exclude as many excipient particles as possible

### Raman Confirmation

- Perform Raman measurements on selected particles for chemical identification.



# MDRS



Research on development, optimization, and validation of MDRS methods

- Nasal Spray Suspensions
- Dry Powder Inhalers
- Transdermal Systems, Ophthalmic Ointment, Cream



1. Q. Liu, M. Absar, B. Saluja, C. Guo, B. Chowdhury, R. Lionberger, D. Conner, B. Li, Scientific Considerations for the Review and Approval of First Generic Mometasone Furoate Nasal Suspension Spray in the United States from the Bioequivalence Perspective, *The APPS Journal*, 2019.
2. B. Thomas, M. Absar, R. Devadia, D. Conti, K. Witzmann, C. Guo, Analytical Method Development for Characterizing Ingredient-Specific Particle Size Distributions of Nasal Spray Suspension Products, *J. Pharm. Sci.*, 110 (2021) 2778–2788

# Summary



- Inhalation drug testing and research is an integral part of OPQR's work.
- OPQR's laboratory-based research programs
  - Provide data to support guidance development
  - Facilitate evaluation of generic drug applications
  - Allow for risk-based assessments of new drugs

# Acknowledgements

## OPQ/OPQR Inhalation Team

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- Nashwa El-Gendy

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- Markham Luke
- Ross Walenga
- Elizabeth Bielski
- Susan Boc

## OGD/OB Collaborators

- Bing Li
- Ke Ren

# Challenge Question #1



**Which city is the OPQR inhalation lab located?**

- A. Rockville, MD
- B. Silver Spring, MD
- C. Washington, DC
- D. Saint Louis, MO

# Challenge Question #2



Which of the following technique/method is **NOT** considered as an alternative BE approach for assessment of inhalation products?

- A. Realistic APSD
- B. Solid-state Nuclear Magnetic Resonance
- C. Clinically relevant dissolution
- D. Particle morphology