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

Changning Guo, PhD

Supervisory Chemist, DPQR II, OPQR | OPQ | CDER | US FDA

September 24, 2024


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.

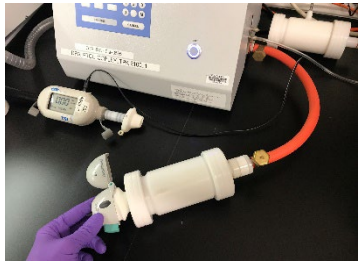
OPQR Labs

Center for Drug Evaluation and Research (CDER)

- Office of Pharmaceutical Quality (OPQ)
  - Office of Pharmaceutical Quality Research (OPQR)

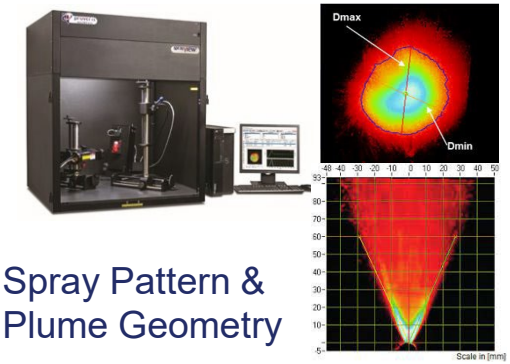
Division of Pharmaceutical Quality Research II (DPQR II)
- Saint Louis, MO
- 1 of the 6 divisions under OPQR

Inhalation Lab Capability



Delivery Dose Uniformity (DDU)

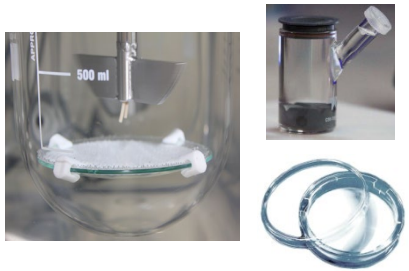
Aerodynamic Particle Size Distribution (APSD)



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

Realistic Aerodynamic Particle Size Distribution (APSD)

Bio-Relevant Mouth-Throat Models

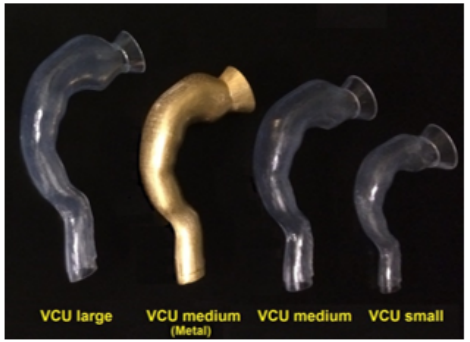
USP Throat

Alberta Idealised Throat (AIT)

Commercial product

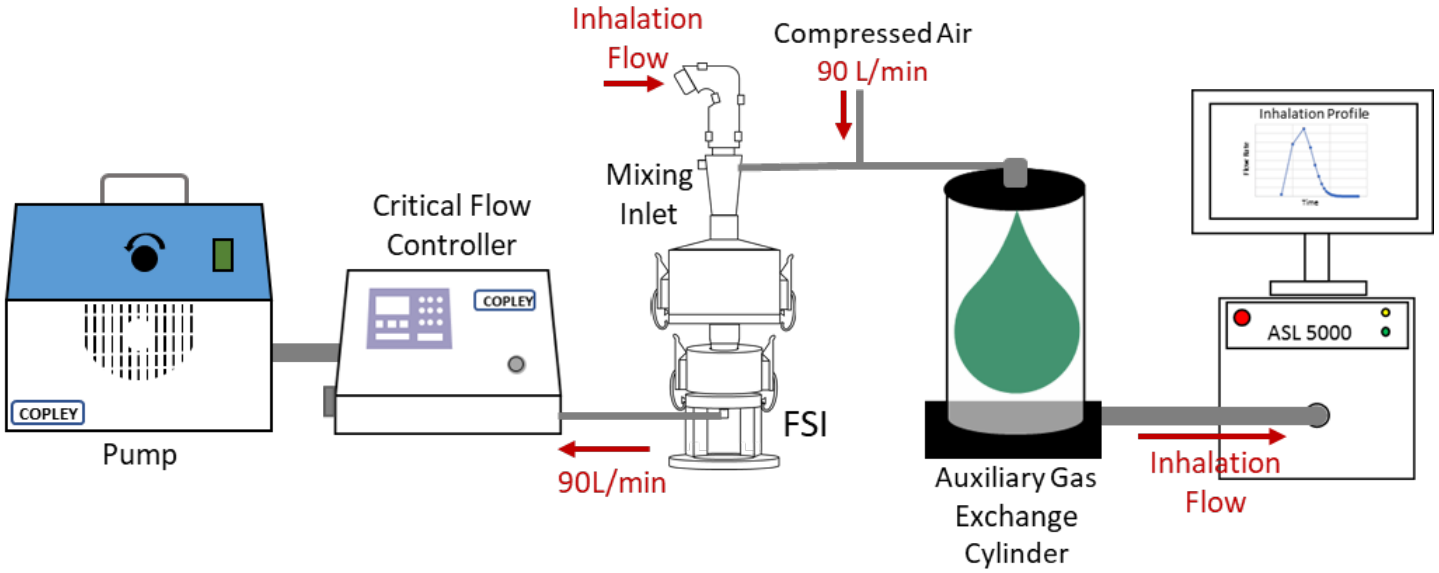
Virginia Commonwealth University (VCU) models

3D printed



Reference:
www.rddonline.com/resources/tools/models.php

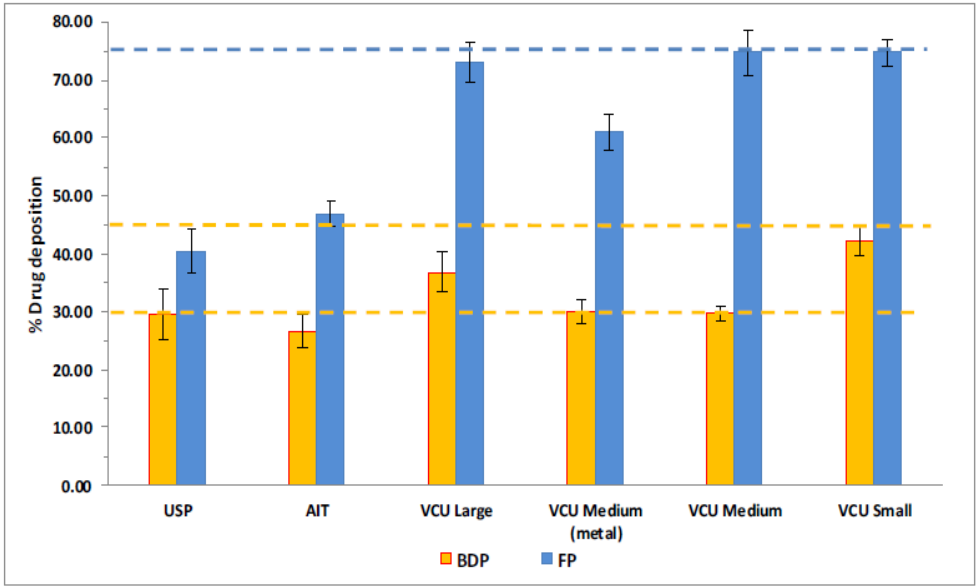
Realistic Breath Simulation



Schematic of realistic breath simulation experimental setup for DPI evaluation

Bio-Relevant Mouth-Throat Models

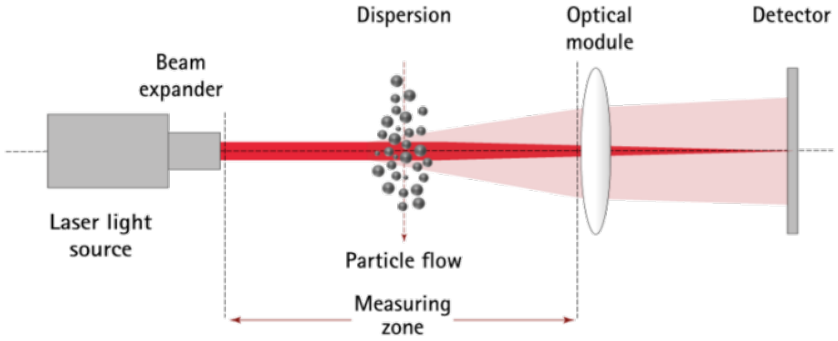
MT deposition (% emitted dose)



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

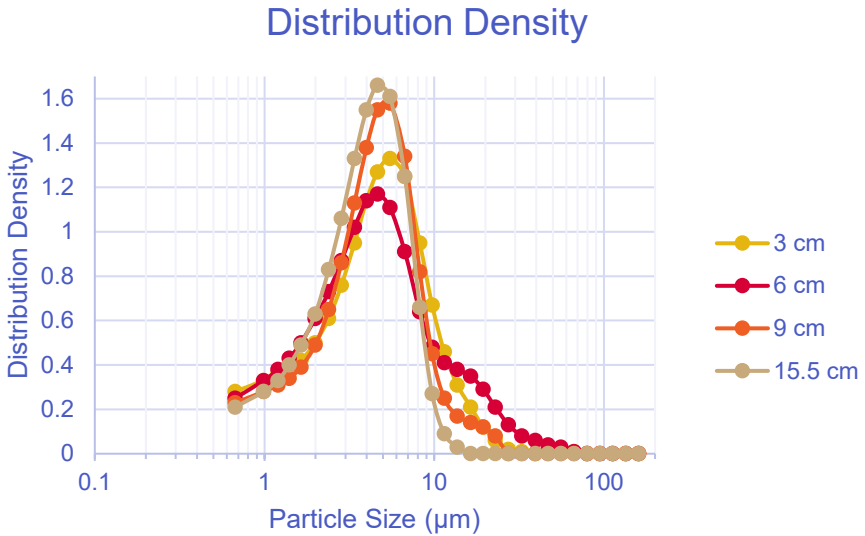


- Pros:
  - Rapid Measurements
- Cons:
  - Measures volume-based PSD, not Aerodynamic PSD
  - Not able to differentiate APIs and excipients

Example for Supporting PSG

Soft Mist Inhaler

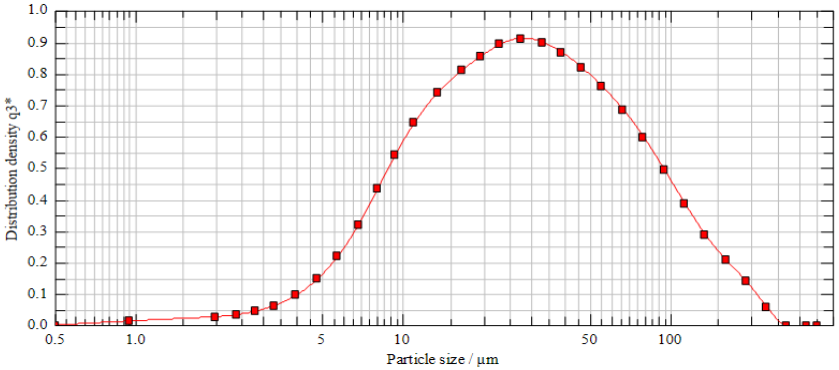
Spiriva Respimat

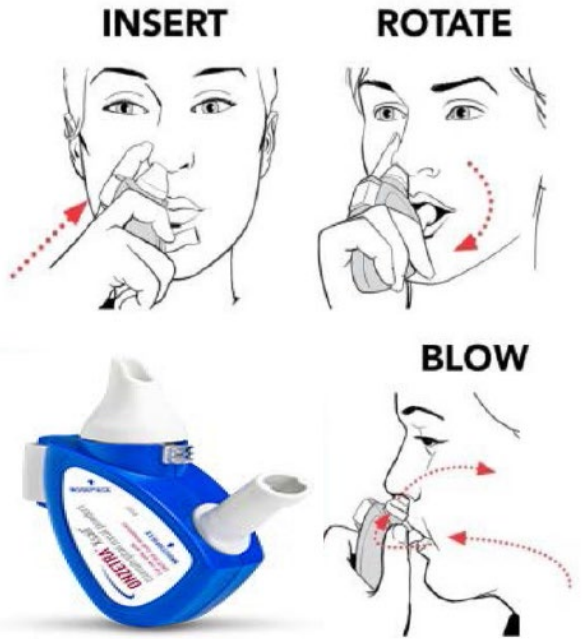


Example for Supporting PSG

Breath-Actuated Nasal Powder

- Onzetra Xsail

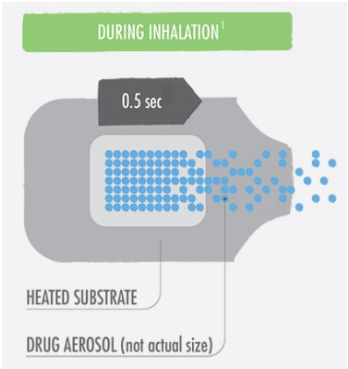


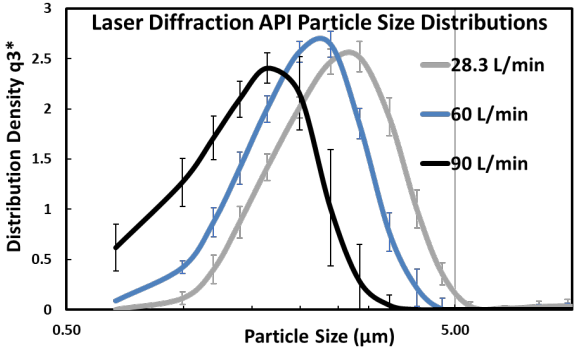


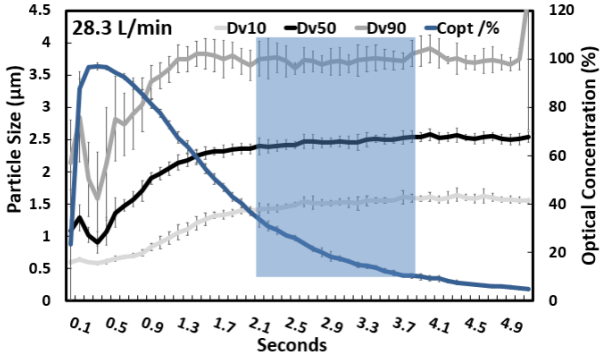
Example for Supporting PSG

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

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

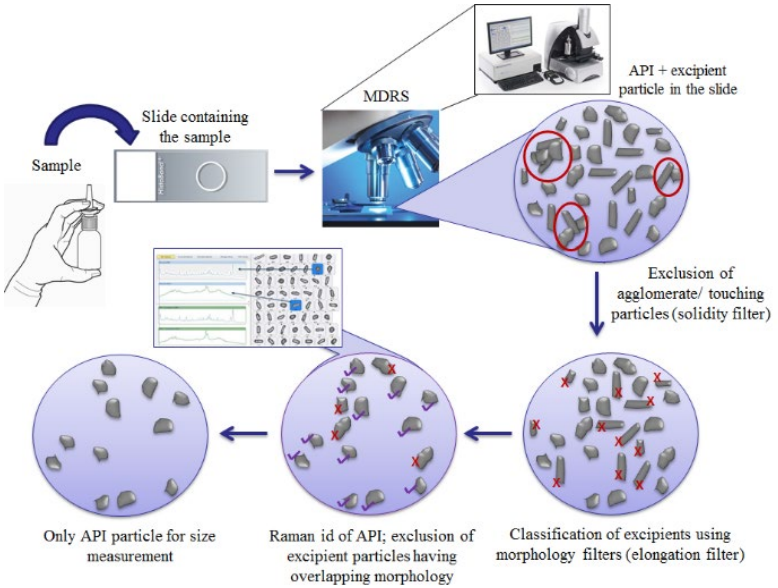
A Raman microscopy system designed for particle sizing characterization

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

- Nicholas Holtgrewe
- Xiaofei Liu
- Nathan Reed
- Anubhav Kaviratna *
- Brandon Thomas *

OPQ/OPQA Collaborators

- Dhaval Gaglani
- Nashwa El-Gendy

OGD/ORS Collaborators

- Bryan Newman
- 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