Challenges with Method Standardization for Inhalation and Nasal Drug Products

Fiscal Year (FY) 2025
Generic Drug Science and Research Initiatives Public Workshop
Day 1, Session 2: Tackling Product Complexity Through In Vitro and In Silico Approaches
June 3, 2025

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Disclaimer

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Inhalation and Nasal Drug Products:
Demonstrating Bioequivalence

Recently recommended and revised product-specific guidances (PSGs) on locally acting inhalation and nasal drug products[1] have focused on providing an additional option to demonstrating bioequivalence (BE) of test products to the reference standard.

- Option-based approach:
  - Option 1: formulation sameness language and an *alternative approach* to the comparative clinical endpoint (CCEP) BE study
  - Option 2: traditional weight-of-evidence approach that includes a CCEP BE study
- Alternative approach studies may include:

Study Type	Inhalation	Nasal
In vitro BE	• **Realistic Aerodynamic Particle Size Distribution (rAPSD)** • **Dissolution**	• Drug particle size distribution • **Dissolution**
In vivo BE	• PK BE study with charcoal block	
Comparative characterization	• **Particle morphology of the emitted dose** • **Polymorphic form of the drug substance** • **Evaluation of crystalline and amorphous content of the formulation**	
Optional	• Computational model(s) for regional drug delivery	

➢ ***General recommendations are provided since there are still many ongoing questions***

Inhalation and Nasal Drug Products:
Dissolution

Background

Dissolution can provide understanding of how active pharmaceutical ingredients (APIs) may dissolve and are available for absorption, a critical aspect that influences the bioavailability (BA) of the API at the site of action. This is particularly true for poorly soluble or dissolution-limited APIs.

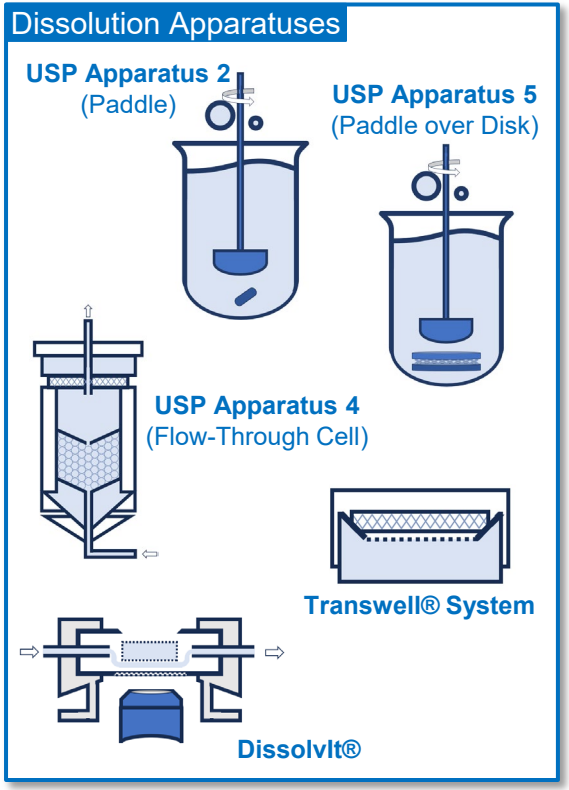
General recommendations

An appropriate apparatus may be used to determine dissolution measurements using a sufficiently developed and validated method to support its sensitivity in detecting differences in performance between test and reference standard products.

BE based on: Comparative analysis of dissolution profiles using an appropriate statistical method.

Ongoing Challenges

- Standardization of sample collection method (e.g., size-fractionated, representative lung deposited dose, total dose) and dissolution apparatus (including considerations for selection, e.g., sink or non-sink conditions)
- Discriminatory and/or biopredictive/biorelevant method development
- Additional statistical methods appropriate to determine BE



Inhalation Drug Products:
Realistic APSD

Background

Realistic APSD provides assurance of comparable total lung deposition, and some assurance of comparable regional lung deposition based on similarity in APSD for more clinically relevant conditions and considerations of patient variability.

General recommendations

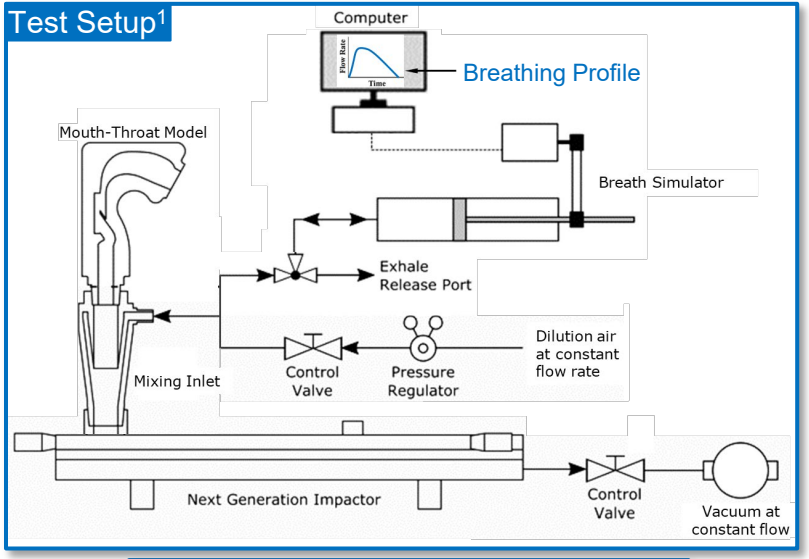
The realistic APSD test should be performed using…breathing profiles (e.g., weak and strong) that are representative of the entire patient population.

BE based on: Population BE or other appropriate statistical analysis of impactor-sized mass for each mouth-throat model-breathing profile combination.

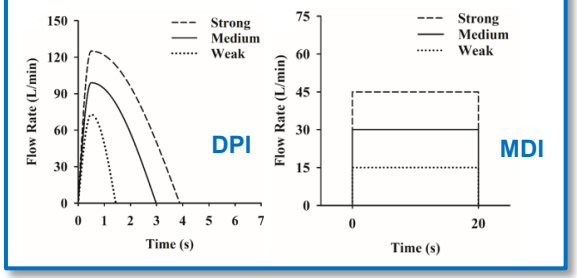
Ongoing Challenges

- Selection of inhalation profiles and relevance of dosage form
- Considerations for mass balance and methods to reduce variability
- Correlation of APSD parameters with in vivo performance
- Additional statistical methods appropriate to determine BE

Test Setup[1]



Breathing Profiles[2]



Inhalation Drug Products:
Comparative Characterization

Background

Particle morphology (e.g., shape, surface roughness, porosity, crystalline/amorphous structure, agglomeration, etc.) of the residual drug particles, once deposited in the lungs, may impact product characteristics that affect BA at the site of action (e.g., dissolution rate, cellular permeability, and uptake within the lungs).

General recommendations

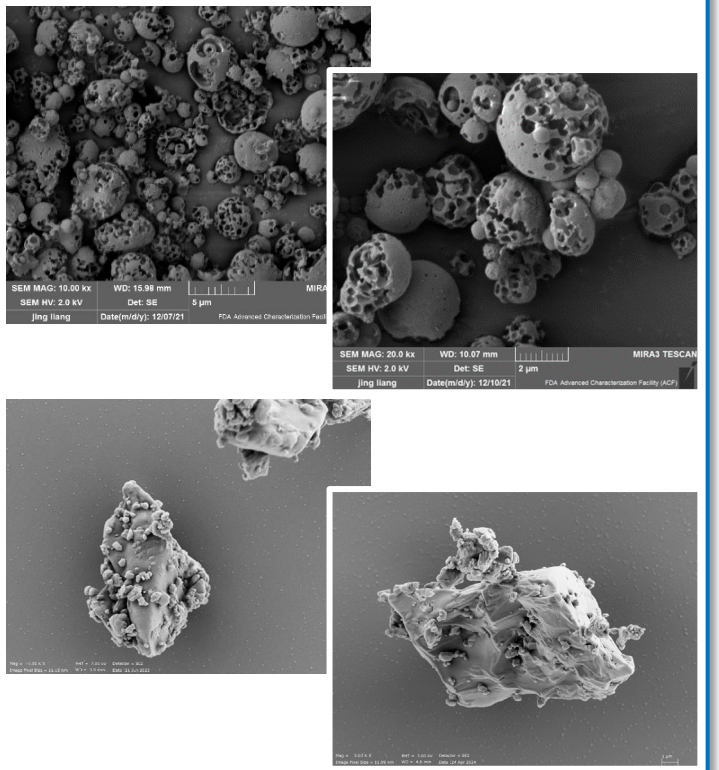
Comparative physicochemical characterization studies should include:

- *Polymorphic form of the drug substance*
- *Particle morphology of the emitted dose*
- *Evaluation of the crystalline and amorphous content of the formulation*

Ongoing Challenges

- Appropriate techniques for characterization
- Sample collection and/or preparation
- Clinical relevance to performance
- Quantitative and statistical analyses

Morphological Characterization



Current Grants and Contracts[3,4]

- DissolvIt – An In Vitro Test Model Built to Resemble Relevant Lung Physiology for Evaluating the Dissolution and Absorption of Drugs Administered via the Inhalation Route (Contract 7F40122C00197)
- Research Challenges Related to Environmentally Friendly Propellants In Metered Dose Inhalers (Contract 75F40123C00186)
- Developing a Regulatory Framework for Emerging Pulmonary Drug Delivery Technology through Morphological and Performance Evaluation of Spray-Dried Phospholipid Porous Particles (Grant ORS-INT-2022-02-A)
- Development of a Laser-Based Testing Platform for Dry Powder Inhaler (DPI) Evaluation and In-Silico Model Validation (Contract 75F40123C00201)
- Identification of Drug Distribution in Aerosols: A Nanospectroscopy and Nanothermal Analysis (Contract 75F40122C00202)

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Research to study the use of a more biorelevant **dissolution** apparatus

- Research Challenges Related to Environmentally Friendly Propellants In Metered Dose Inhalers (Contract 75F40123C00186)

Studies with **realistic mouth-throat models** that can facilitate study optimization and reduce potential method variability

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Research using various imaging techniques that can aid **comparative characterization** study method optimization, analyses method development, and understanding on relevance to clinical performance

Completed Research[5,6]

Journal of Aerosol Science 179 (2024) 106387

Contents lists available at ScienceDirect

Journal of Aerosol Science

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In vitro evaluation of intersubject variability in pediatric intranasal drug delivery using nasal spray suspension products

Amir R. Esmaeili [a], John V. Wilkins [a], Sana Hosseini [a], Ali Alfaifi [a], Mohammad Hejazi [a], Michael Hindle [b], Worth Longest [a,b], Theodore Schuman [c], Sneha Dhapare [d], Anubhav Kaviratna [d], Ross Walenga [e], Bryan Newman [d], Laleh Golshahi [a,*]

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International Journal of Pharmaceutics 666 (2024) 124743

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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Anatomically-detailed segmented representative adult and pediatric nasal models for assessing regional drug delivery and bioequivalence with suspension nasal sprays

Prakash Khadka [a], Mohammad Hejazi [a], Michael Hindle [b], Theodore Schuman [c],
[a,b], [d], [e], [e], Bryan Newman [d],

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Research developed adult and pediatric in vitro nasal models used to evaluate regional deposition of nasal spray products with the typical spray device design

Potential remaining research gaps:

- Use of in vitro models to evaluate nasal spray products with more complex device designs or location for deposition
- Implementation of in vitro models to support BE assessments

Summary

- There are still ***ongoing challenges*** regarding specific recommendations for alternative studies provided in product-specific guidances for demonstrating bioequivalence
  - Dissolution challenges related to method development and statistical analysis
  - Realistic APSD challenges related to breathing profiles, variability in data, correlation with in vivo performance, and additional methods for statistical analysis
  - Comparative characterization challenges related to methods, sample collection, discriminatory ability, quantitative analysis, and relevance to in vivo performance
- There is ongoing and recently completed research in these areas; however, potential gaps still exist.

Acknowledgements

- FDA/CDER/OGD/ORS
  - Elizabeth Bielski
  - Steven Chopski
  - Liangfeng Han
  - Anubhav Kaviratna
  - Rama Kashikar
  - David McChesney
  - Abhinav Mohan
  - Eleftheria Tsakalozou
  - Ross Walenga
  - Bryan Newman
- FDA/CDER/OTS/OCP
  - Sneha Dhapare
- FDA/CDER/OGD/ORS
  - Yan Wang
  - Markham Luke
  - Lei Zhang
  - Robert Lionberger
- FDA/CDER/OPQ/OPQR
  - Nathan Reed
  - Jafrin Jobayer Sonju
  - Qi Wang
  - Yang Yang
  - Yuan Zhang
  - Changning Guo
  - Xioaming Xu


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