Orally Inhaled Drug Product PSGs: General Considerations Using the Alternative Bioequivalence (BE) Approach In Lieu of Comparative Clinical Endpoint (CCEP) BE Study for Suspension-Based Metered Dose Inhalers

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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Learning Objectives

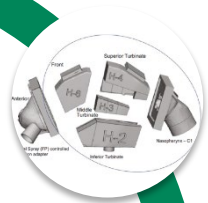
- Recognize the challenges with conducting comparative clinical endpoint (CCEP) bioequivalence (BE) studies for orally inhaled drug products (OIDPs).
- Describe the available tools, supportive FDA research, and external input for developing alternative BE approaches.
- Identify recently developed product-specific guidances (PSGs) for suspension-based metered dose inhalers (MDIs) with alternative BE approaches to the CCEP BE study and study design considerations.

The Challenges with CCEP BE Studies

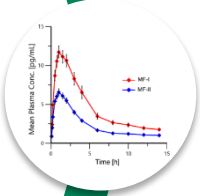
- FDA traditionally recommends CCEP BE studies as part of a BE assessment for locally-acting MDIs and DPIs.
- CCEP BE studies can pose several **challenges** for generic applicants developing an MDI or DPI.
  - ***Higher variability*** → ***lower accuracy*** *and* ***reproducibility***
  - ***Flat exposure-response*** → ***lower sensitivity***
- Ultimately, these challenges necessitate using **large numbers** of patients often over a **long study duration**.
  - ***Costly***
  - ***Time Consuming***

CCEP BE Studies

Alternative BE Approaches



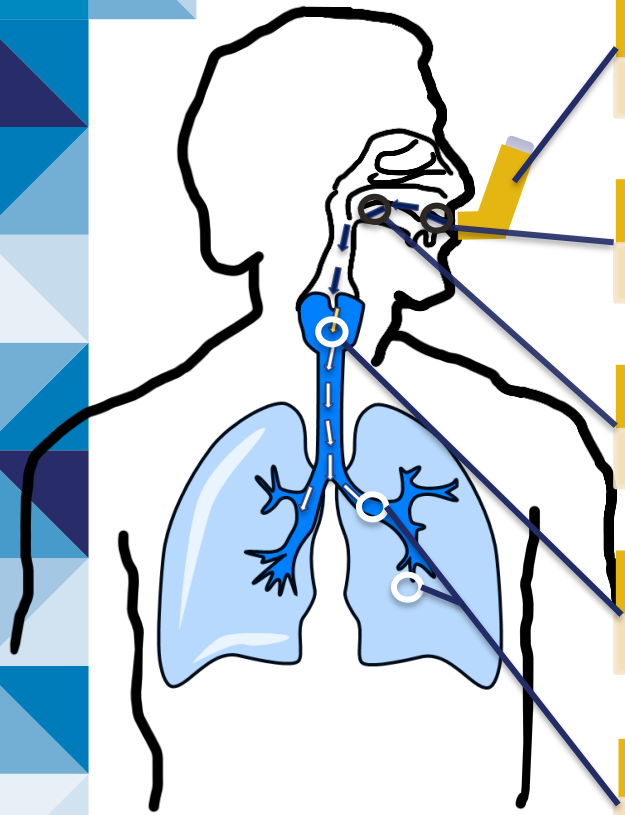
In Vitro Methods



In Vivo Methods

In Silico Methods

Potential Methods for Assessing Contributing Factors to Local Drug Delivery



Step 1
Formulation/Device Characteristics

Step 2
Actuation and Aerosolization

Step 3
Formulation Post-Actuation

Step 4
Airway Transit

Step 5
Deposition, Dissolution, Absorption

IN VITRO STUDY METHODS

- Realistic Aerodynamic Particle Size Distribution (APSD)
- Dissolution
- Optical Suspension Characterization
- Droplet Size Distribution by Laser Diffraction
- Morphology-assisted Raman Spectroscopy (MDRS)
- Scanning Electron Microscopy (SEM)
- X-ray Tomography
- Shadowgraphic imaging/shadow motion analysis
- Phase Doppler Interferometry/Anemometry
- Particle Imagine Velocimetry
- Optical Photothermal Infrared Microscopy
- Atomic Force Microscopy – Infrared Microscopy
- Cell Permeability Assays

IN VIVO STUDY METHODS

- Charcoal Block PK Study
- Imaging-based Study (e.g., Scintigraphy)

IN SILICO STUDY METHODS

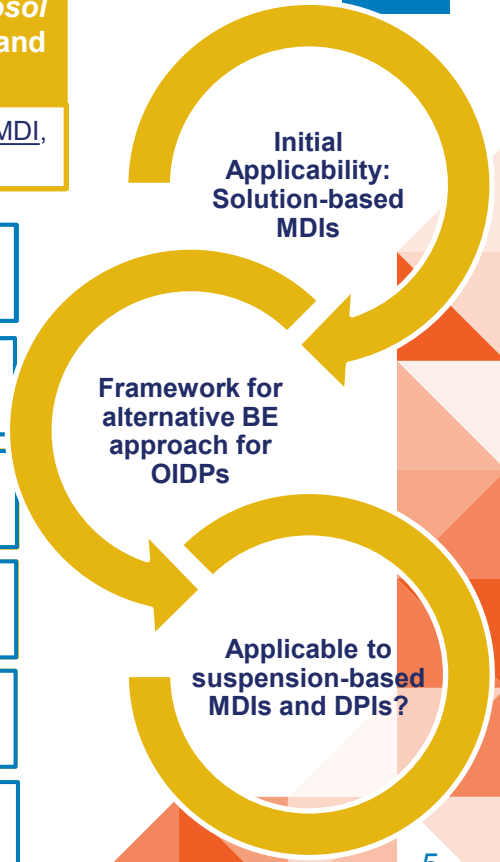
- Computational Fluid Dynamics (CFD)
- Regional Deposition Modeling
- Physiologically Based PK modeling (PBPK)
- Population PK Modeling

Alternative BE Approach: Solution MDIs

Product-specific guidances (PSGs) on *Beclomethasone Dipropionate Metered Inhalation Aerosol* (NDA 020911; NDA 207921), *Ipratropium Bromide Metered Inhalation Aerosol* (NDA 021527), and *Ciclesonide Metered Inhalation Aerosol* (NDA 021658)

If a generic demonstrates formulation sameness (qualitative and quantitative) and device similarity to the reference MDI, FDA recommends additional supportive studies to help ensure ***equivalence at the local site of action*** (i.e., lungs):

Actuation, Aerosol formation	**Characterization of Emitted Sprays** (velocity profiles and evaporation rates) • Understand emitted droplet size and evaporation process of formulation (volatiles + non-volatiles)
Formulation Post-actuation	**Morphology Imaging Comparisons** (characterization of full range of residual drug particle sizes) • Understand residual particle morphology and size distribution of emitted formulation
Transit through the airways; Deposition, Dissolution, Absorption	**More Predictive APSD Testing** (representative mouth-throat models and breathing profiles) • Understand impact of patient variability
	Dissolution • Understanding how drug(s) dissolves at the site of action for absorption once deposited
Methods for further support	**Quantitative Methods and Modeling** (e.g., PBPK, CFD studies) • IVIVCs to bridge gap between in vitro product performance and regional drug deposition
	Alternative PK BE Studies • Understanding how PK studies may correlate to local deposition



External Input Informs FDA Thinking on Alternative BE Approaches for OIDPs

CENTER FOR RESEARCH ON COMPLEX GENERICS

FDA U.S. FOOD & DRUG ADMINISTRATION

- **Two-day workshop** to discuss the Agency's ***scientific understanding and regulatory perspective on alternative BE approaches*** with industry representatives and academic experts.
- In-person attendees participated in small group discussions that provided FDA with valuable insight into the ***industry's experiences*** with alternative BE approaches and their thinking on potential approaches for complex OIDPs (suspension MDIs and DPIs).

https://www.complexgenerics.org/education-training/considerations-for-and-alternatives-to-comparative-clinical-endpoint-and-pharmacodynamic-bioequivalence-studies-for-generic-orally-inhaled-drug-products-2/

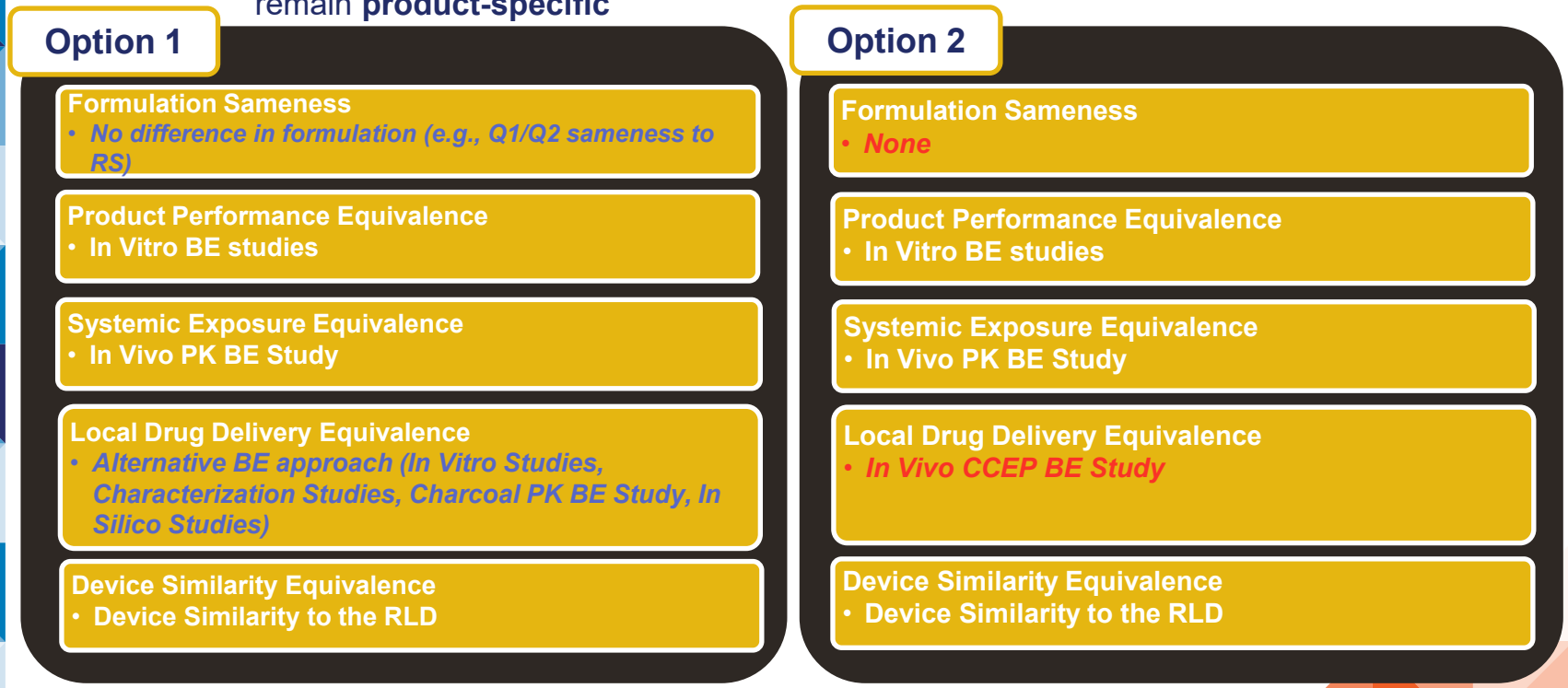
External Input Informs FDA Thinking on Alternative BE Approaches for OIDPs

- Most **alternative approaches** are generally ***applicable to both MDIs and DPIs*** irrespective of their formulation.
- Certain approaches are ***more critical and informative.***
- Inclusion of a particular study may be ***product-specific*** (e.g., dependent on the drug substance properties).
- Some approaches useful for ***product development*** vs. others for assessing **BE.**

Useful Study Methods	• Realistic APSD • Dissolution • In silico methods
Potentially Useful or Confirmatory	• Particle morphology • Charcoal-block PK study
Study Methods with Limited Utility	• Evaporation rate and velocity profile evaluation • Pre-actuation characterization of the formulation

Implementing the Agency's Current Thinking for Suspension MDIs

- Recent suspension-based MDI PSGs: ***option-based approach*** for establishing BE
  - Specific study designs (e.g., supportive characterization studies or optional components) remain **product-specific**



Q1: qualitative; Q2: quantitative

RS: reference standard; RLD: reference listed drug

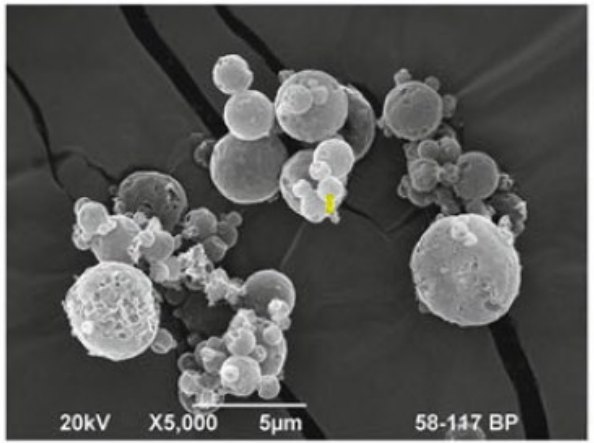
Implementing the Agency's Current Thinking for Suspension MDIs

BEVESPI AEROSPHERE
Formoterol Fumarate; Glycopyrrolate Metered Inhalation Aerosol

BREZTRI AEROSPHERE
Budesonide; Formoterol Fumarate; Glycopyrrolate Metered Inhalation Aerosol

- **Formulation:** co-suspension formulation of drug particles and phospholipid-based porous particles in propellant.
  - **Porous particles:** 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and calcium chloride

- ***FDA-approved suspension-based MDIs***
- **Indication:** the maintenance treatment of patients with chronic pulmonary obstructive disease (COPD).



An example of phospholipid-based porous particles utilized in several MDI products.

Suspension MDI PSGs Incorporating Alternative BE Approaches

Draft Suspension MDI PSGs (Feb 2024)

- *Formoterol Fumarate; Glycopyrrolate Inhalation Aerosol, Metered*
- *Budesonide; Formoterol Fumarate; Glycopyrrolate Inhalation Aerosol, Metered*

Draft Suspension MDI PSGs (Aug 2024)

- *Fluticasone Propionate Inhalation Aerosol, Metered*
- *Fluticasone Propionate; Salmeterol Xinafoate Inhalation Aerosol, Metered*
- *Albuterol Sulfate Inhalation Aerosol, Metered*
- *Levalbuterol Tartrate Inhalation Aerosol, Metered*

Option 1 BE Approach

- **Formulation**
  - The test (T) product should contain ***no difference in inactive ingredients or other aspects of the formulation*** relative to the RS that may affect local or systemic availability (e.g., Q1/Q2 formulation sameness)
- **In Vitro BE Studies**
  - SAC, APSD, spray pattern, plume geometry, priming/repriming
  - ***Realistic APSD (rAPSD)***
  - ***Dissolution****
- **Comparative Characterization Studies**
  - **Particle Morphology of the Emitted Dose**
- **In Vivo Studies**
  - In Vivo PK BE Study
  - ***In Vivo PK BE study with Charcoal Block***
- **Additional Information**
  - Optional Computational Modeling study
  - Device similarity to the RLD

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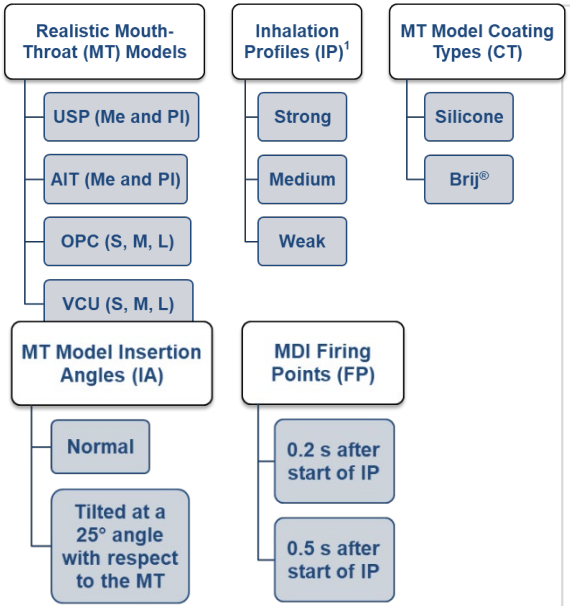
- *Levalbuterol Tartrate Inhalation Aerosol, Metered*

Option 2 BE Approach

- **Formulation**
  - ***No recommendations provided (e.g., T product formulation can be Q1/Q2 or non-Q1/Q2 to RS formulation)***
- **In Vitro BE Studies**
  - SAC, APSD, spray pattern, plume geometry, priming/repriming
- **Comparative Characterization Studies**
  - Particle Morphology of the Emitted Dose
- **In Vivo Studies**
  - In Vivo PK BE Study
  - ***CCEP BE study in subjects with asthma***
- **Additional Information**
  - Optional Computational Modeling study
  - Device similarity to the RLD

Realistic APSD Study Design Considerations

- **GDUFA-Funded Research Outcomes**
  - Response to the various study factors is ***product-specific.***
  - **Method Development:** consider mouth-throat (MT) types and size, inhalation profiles (IPs), and other factors.



Study design factors evaluated for rAPSD with solution and suspension-based MDIs.

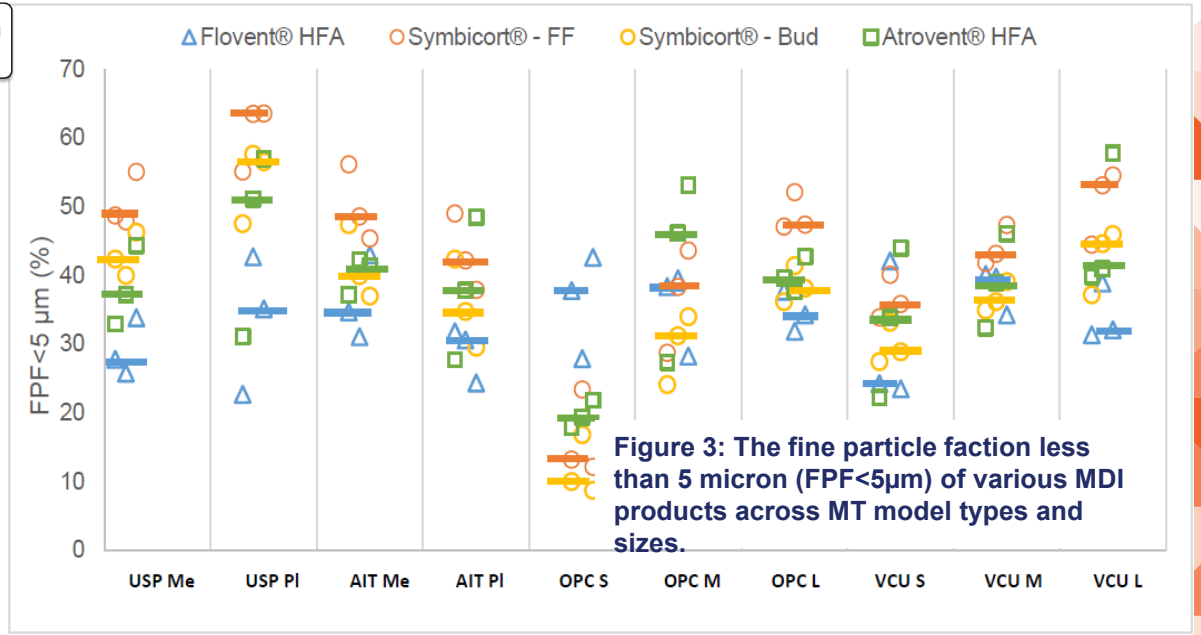
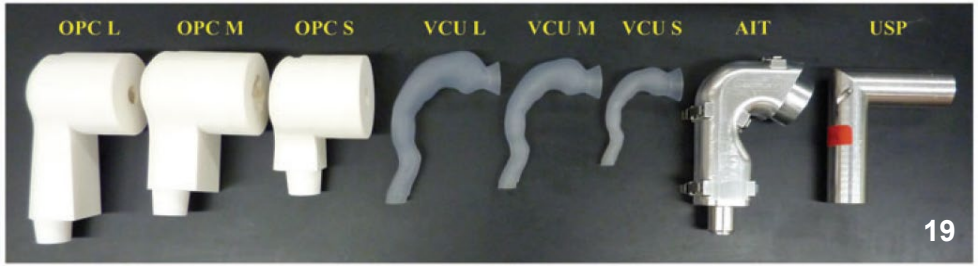


Figure 3: The fine particle faction less than 5 micron (FPF<5µm) of various MDI products across MT model types and sizes.

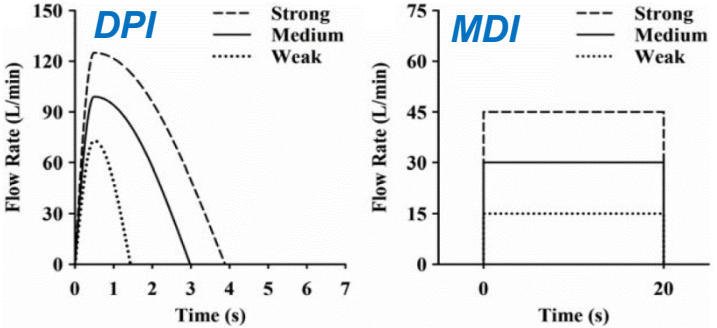
USP: United States Pharmacopeia; AIT: Albert Idealized Throat; OPC: Oropharyngeal Pharmacopeia Consortium; VCU: Virginia Commonwealth University

Realistic APSD Study Design Considerations

Realistic mouth-throat (MT) models

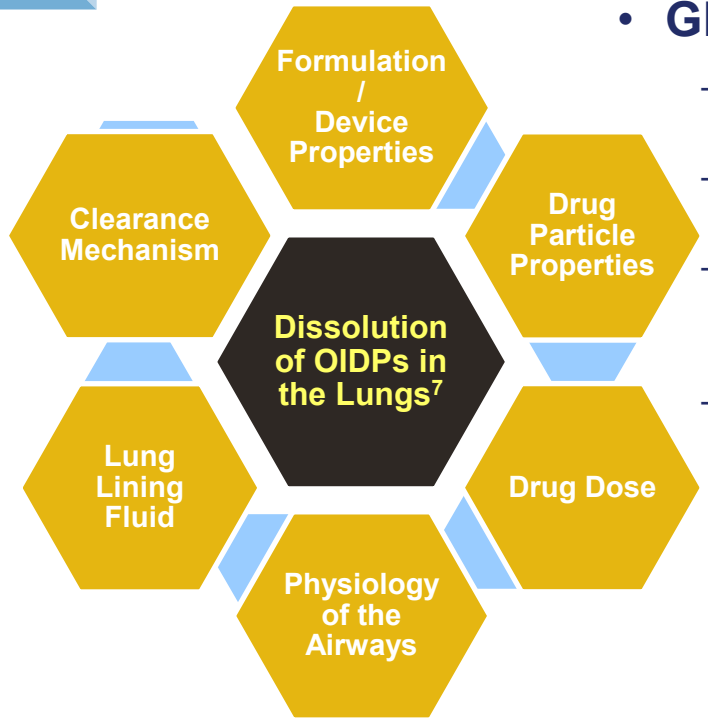


Inhalation profiles (IPs)



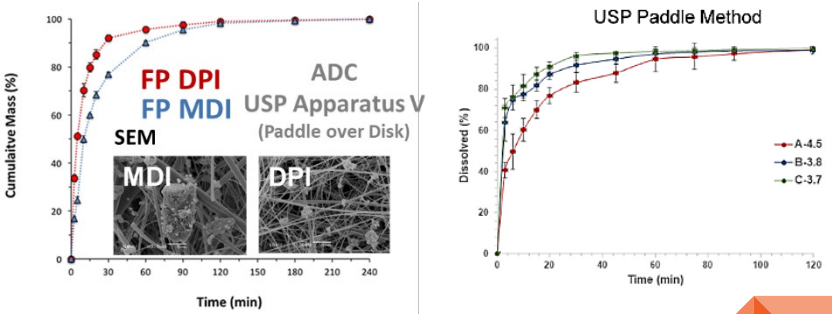
- **PSG Recommendations:**
  - **Beginning** lifestage.
  - Include different ***MT sizes*** and ***IPs*** that reasonably cover the expected inter-subject variability of the indicated patient population via **bracketing approach.**
    - Example: Small and large MT sizes + weak and strong IPs the cover patient population.
    - Correlate in vitro performance to in vivo lung deposition data, if available.
    - IPs obtained from patients.
  - **BE**: ***population bioequivalence (PBE)*** of ***impactor sized mass (ISM)*** for each MT model-IP combination.
    - ***Alternative statistical approaches*** may be used if scientifically justified.
    - Request a ***Pre-ANDA meeting*** to discuss **alternative approaches** to the study design and/or statistical methods.

Dissolution Study Design Considerations for OIDPs



Drug dissolution in the lungs can be impacted by multiple factors.

- **GDUFA-funded research**
  - **Many contributing factors** that can affect ***dissolution performance*** and ***study sensitivity.***
  - Currently **no** standardized method; method development is ***product-specific.***
  - Can develop dissolution methods that are **sensitive** and **discriminatory** to meaningful differences in ***formulation*** and/or ***manufacturing process.***
  - The need for dissolution studies is ***drug-*** (e.g., high/low solubility) and ***product-specific.***



Dissolution of OIDPs are sensitive to differences in both dosage form (left) and particle size (right).

Dissolution Study Design Considerations for OIDPs

- **PSG Recommendations:**
  - ***Beginning*** Lifestage.
  - Collect **aerosolized dose** of ***similar drug mass*** between T and RS products.
  - **Optimized** and **validated** method (e.g., apparatus, sample collection, dose, media type and volume, stirring/agitation rate, sampling times).
  - **Discriminatory** (e.g., differences in ***deposited drug particle size***).
  - **BE:** Comparative analysis of dissolution profiles with an appropriate statistical method (e.g., ***similarity [f2] factor***).

Sample Collection

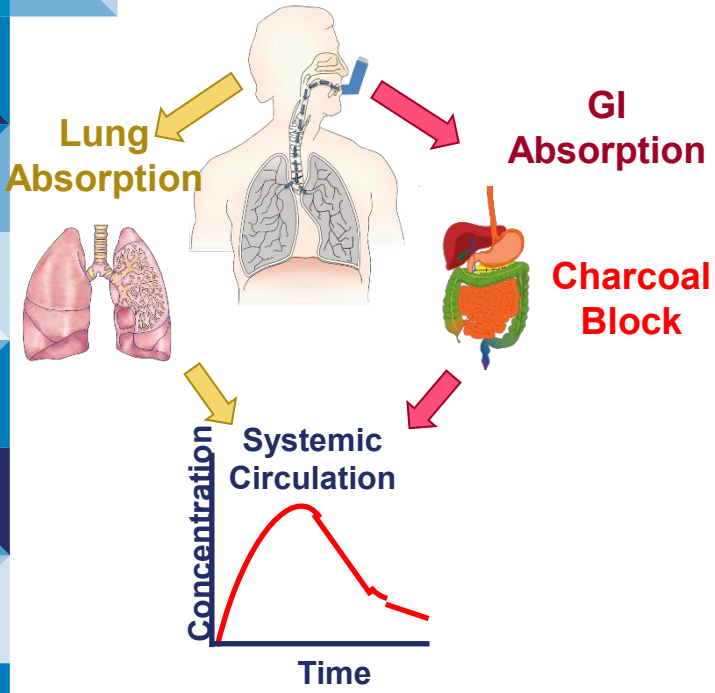
Dissolution Apparatus

Dissolution Media

Method Validation

Assessment

In Vivo Charcoal Block PK BE Study Considerations



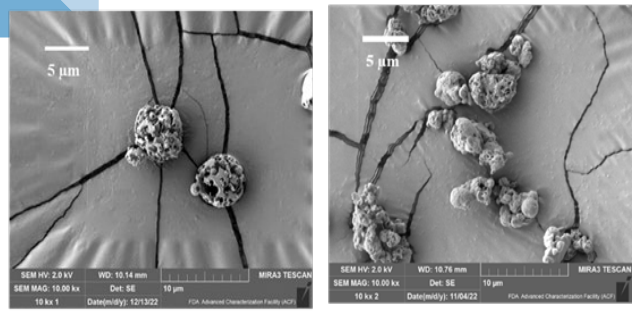
Drug absorption into the systemic circulation following dosing with certain OIDPs can occur through both lung absorption as well as gastrointestinal (GI) absorption. Dosing with charcoal can block GI absorption.

- For OIDPs, a portion of the emitted dose may be swallowed rather than inhaled and end up in the GI tract.
- For drugs with **significant gut absorption**, systemic levels may be difficult to distinguish between inhaled vs. swallowed portions.
- ***Charcoal block PK studies*** allow for a more direct analysis of the lung dose contribution in systemic circulation by eliminating the GI tract dose contribution.

In Vivo Charcoal Block PK BE Study Considerations

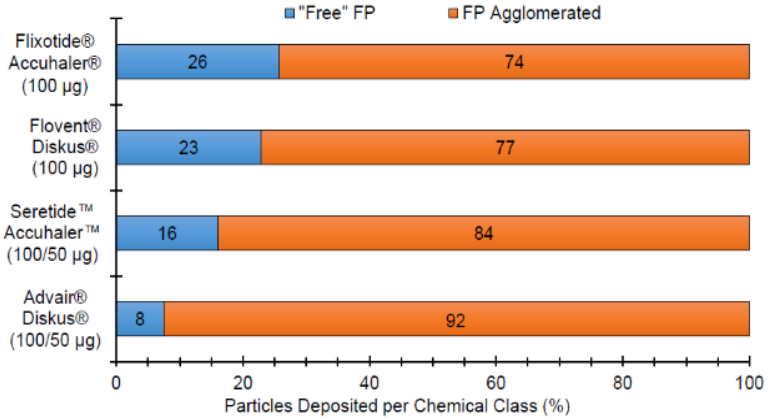
- **PSG Recommendations:**
  - Similar to PK BE study in many aspects.
    - ***Healthy*** adult male and female subjects.
    - ***Minimum number of inhalations*** to sufficiently characterize the PK profile with a sensitive analytical method.
    - Dose administration should follow the approved labeling instructions.
    - ***Bio-IND*** may be needed if the administered dose is **above the maximum labeled single dose**.
  - **No** standard for the ***charcoal dose***, so the selected dose and how and when it is administered should be justified in the ANDA.
  - **BE:** 90% CI for the T/R ratio for AUC and C_{max} being between 80 – 125%.

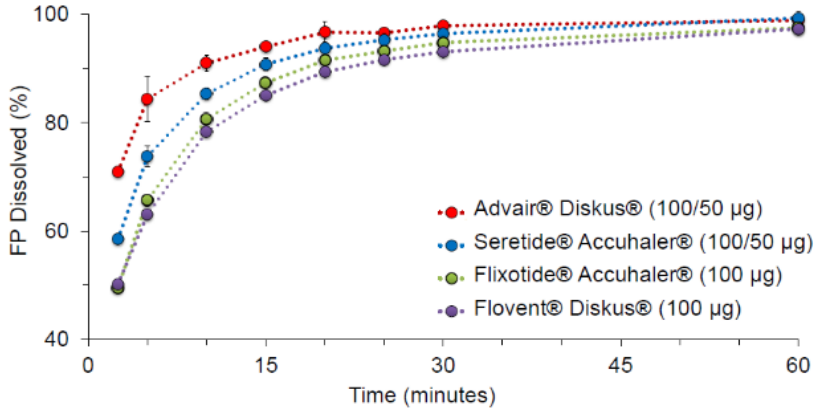
Comparative Characterization Study Considerations



SEM images of phospholipid porous particles found in a marketed DPI (left) and MDI (right)

- ***Comparative characterization studies*** provide **supportive evidence** for establishing BE between T and RS OIDPs.
- For example, particle morphology can contribute to the APSD and dissolution performance for certain OIDPs.
- Whether a PSG for an OIDP incorporates comparative characterization studies depends on the specific product.





Microstructural differences in the deposited particle agglomerates (left) may be one potential contributing factor to performance differences, such as with dissolution performance (right).

Comparative Characterization Study Considerations

- **PSG Recommendations:**
  - A minimum of ***three batches*** each of the T and RS product should be tested using the ***beginning lifestage*** of the product.
  - ***Imaging comparisons*** should be conducted on the deposited particles of the **emitted dose.**
  - The ***morphological features*** of the particles, which may include their **agglomeration characteristics**, should be evaluated.
  - A description of the ***sampling collection method*** should be provided.

Challenge Question #1

Which of the following statements is NOT true?

A. Alternative BE approach can be used in both solution-based and suspension-based MDIs.

B. The studies in the alternative BE approach have distinctive roles of establishing BE.

C. All the studies in the alternative BE approach needed to be conducted for BE establishment for most suspension-based MDIs.

Challenge Question #2

Which of the following statements is true?

A. Either conventional or charcoal block PK BE studies are conducted to establish BE for suspension-based MDIs.

B. Charcoal block PK BE study design is well-established and should be used for all suspension-based MDIs.

C. For suspension-based MDIs with limited GI absorptions, charcoal block PK BE studies may not be necessary.

Summary

- The **challenges** with conducting ***CCEP BE studies*** can lead to **higher costs** and **longer drug development** timelines for generic developers of OIDPs.
- To address these challenges, FDA has explored ***in vitro, in vivo, and in silico study designs*** through GDUFA-funded research initiatives to identify ***alternative approaches*** that can be used in lieu of the CCEP BE study for establishing local drug delivery equivalence.
- Following completion of the ***FDA-CRCG workshop*** on alternative BE approaches for OIDPs in 2023, FDA has utilized the input received from industry and academic attendees to aid the development of several ***PSGs for suspension-based MDIs.***
- These ***developed PSGs*** present FDA's efforts to **expand alternative BE approaches** beyond just solution-based MDIs and highlight the ***additional study considerations*** needed when applying alternative BE approaches to specific drug products.