Recent Updates for the Use of Alternative Approaches for Demonstrating Bioequivalence with OIDPs

PQRI/EUFEPS Global Bioequivalence Harmonisation Initiative: 6th International Workshop – GBHI 2024

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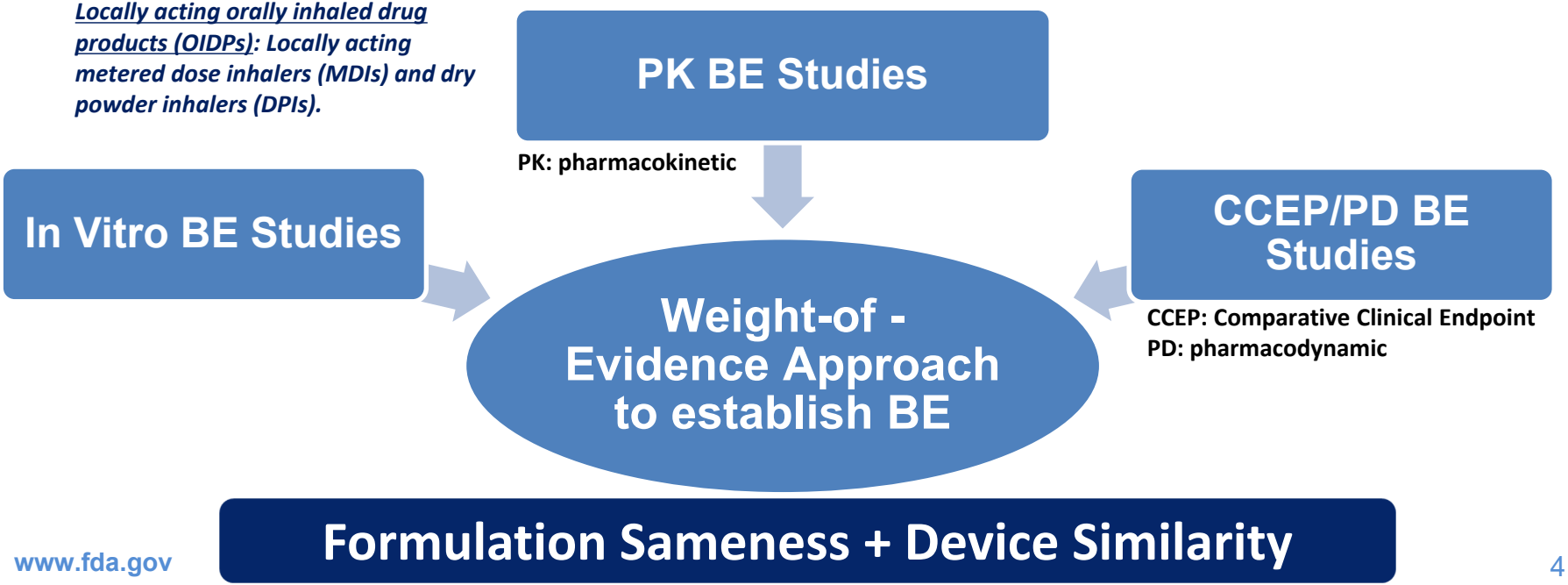
Outline

- Brief overview of the **challenges** with ***conducting comparative clinical endpoint (CCEP) BE studies*** for orally inhaled drug products (OIDPs).
- Exploring the available **tools**, **supportive FDA research**, and **external input** for developing ***alternative BE approaches.***
- Recently developed **product-specific guidances (PSGs)** for ***suspension-based metered dose inhalers (MDIs)*** and ***dry powder inhalers (DPIs)*** with alternative BE approaches to the CCEP BE study and study design considerations.
- Conclusions.

FDA's Historical Approach for Establishment of Bioequivalence (BE) for OIDPs

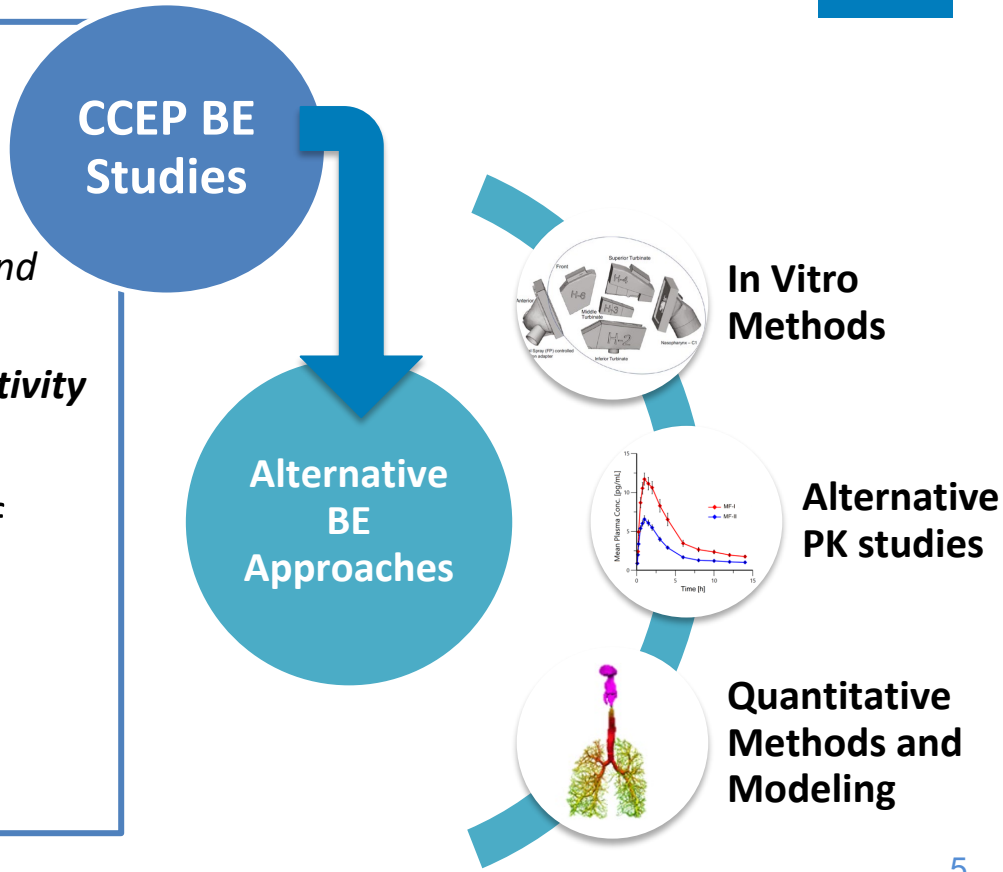
- **Locally Acting BE Establishment**: ***Absence of significant difference*** in which the drug becomes available at the ***site of action (i.e., lungs).***
- **To address challenges for locally acting OIDPs → *Weight-of-Evidence Approach.***

***Locally acting orally inhaled drug products (OIDPs)*: Locally acting metered dose inhalers (MDIs) and dry powder inhalers (DPIs).**

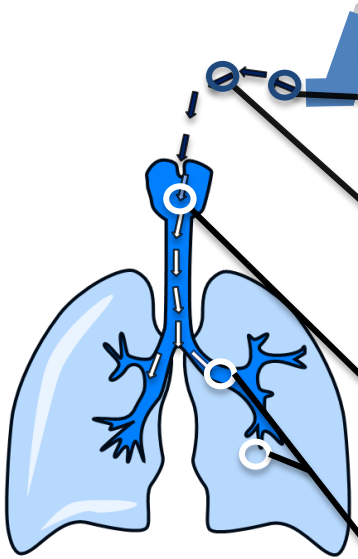


The Challenges with CCEP BE Studies

- 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*



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
- 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

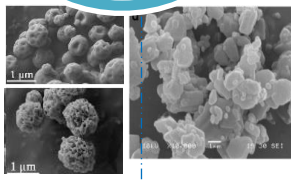
- Charcoal Block Pharmacokinetic (PK) Study
- Imaging – based Study (e.g., Scintigraphy)

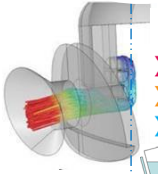
IN SILICO STUDY METHODS

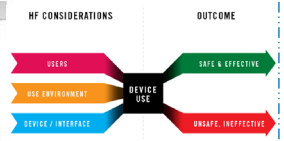
- Computational Fluid Dynamics
- Regional Deposition Modeling
- Physiologically-based PK modeling
- Population PK Modeling

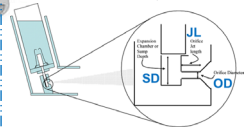
ORS Research Activities for OIDPs

Formulation → Device → User Interface → Regional Deposition → Dissolution → Absorption









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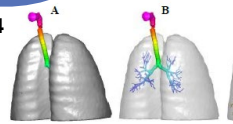

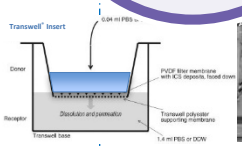

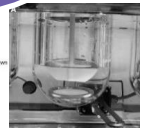

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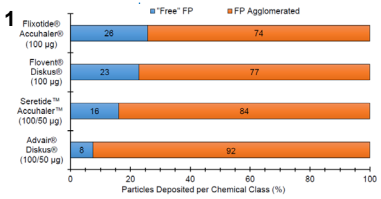

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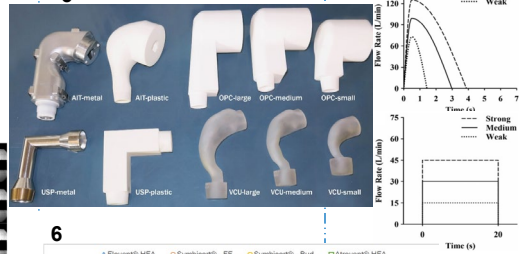

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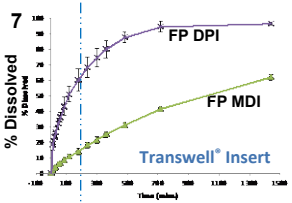

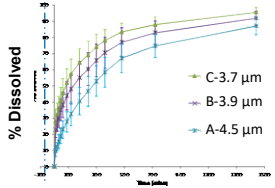

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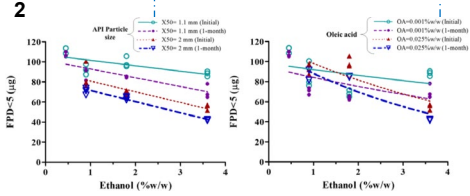

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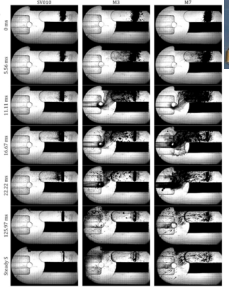

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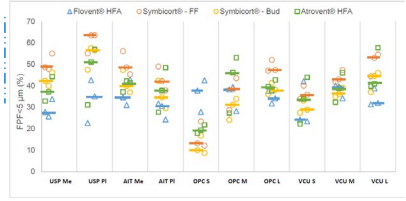

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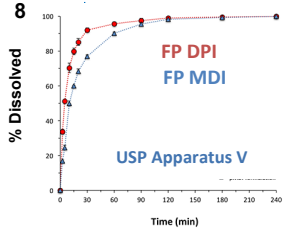

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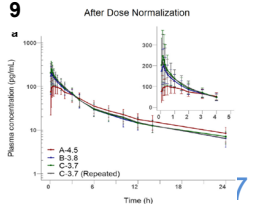


Alternative BE Approach: Solution MDIs

Product-specific guidances (PSGs) on *Beclomethasone Dipropionate Metered Inhalation Aerosol* (NDA 020911; NDA 207921), *Ipratropium Bromide Metered Inhalation Aerosol* (NDA 021757), and *Ciclesonide Metered Inhalation Aerosol* (NDA 021658)

If a generic shows formulation sameness (qualitative and quantitative) and device similarity to the reference MDI, we recommend additional supportive studies to help ensure ***equivalence at the local site of action*** (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

APSD: Aerodynamic Particle Size Distribution

Dissolution
- Understanding how API dissolved at site of action for absorption once deposited

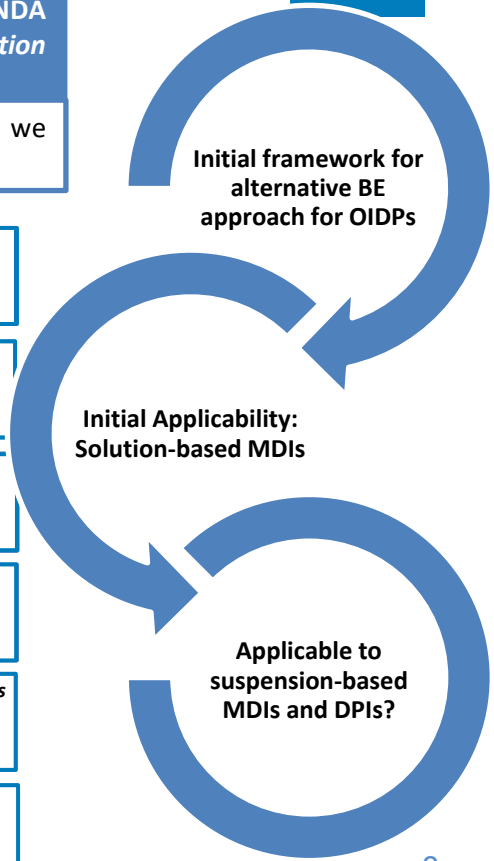
Methods for further support

Quantitative Methods and Modeling (e.g., PBPK, CFD studies)
- IVIVCs to bridge gap between in vitro product performance and regional drug deposition

PBPK: Physiologically-based Pharmacokinetics
CFD: Computational Fluid Dynamics

Alternative PK BE Studies
- Understanding how PK studies may correlate to local deposition

PK: Pharmacokinetics



External Input Informs FDA Thinking on Alternative BE Approaches for OIDPs

Trainings Link: https://www.complexgenerics.org/education-training/
Event Materials: Link.

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).




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

Option 1

Formulation Sameness
- *No difference in formulation (e.g., Q1/Q2 sameness to RS)*

Product Performance Equivalence
- In Vitro BE studies

Systemic Exposure Equivalence
- In Vivo PK BE Study

Local Drug Delivery Equivalence
- *Alternative BE approach (In Vitro Studies, Characterization Studies, Charcoal PK BE Study, In Silico Studies)*

Device Similarity Equivalence
- Device Similarity to the RLD

Option 2

Formulation Sameness
- *None*

Product Performance Equivalence
- In Vitro BE studies

Systemic Exposure Equivalence
- In Vivo PK BE Study

Local Drug Delivery Equivalence
- *In Vivo CCEP BE Study*

Device Similarity Equivalence
- Device Similarity to the RLD

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

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

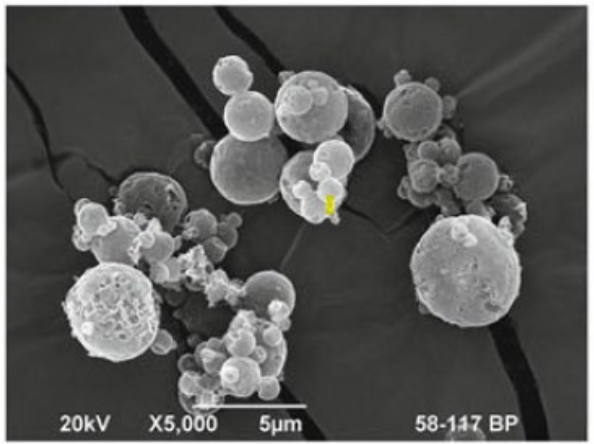


Figure 1: An example of phospholipid-based porous particles utilized in several MDI products.[12]

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

Suspension MDI PSGs Incorporating Alternative BE Approaches

Draft Suspension MDI PSGs (Feb 2024)

Active Ingredients:	Formoterol fumarate; Glycopyrrolate
Dosage Form:	Aerosol, metered
Route:	Inhalation
Strength:	0.0048 mg/inh; 0.0090 mg/inh
Recommended Studies:	Two options: (1) six in vitro bioequivalence studies, one comparative characterization study, and two in vivo bioequivalence studies with pharmacokinetic endpoints, or (2) five in vitro bioequivalence studies, one comparative characterization study, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

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Active Ingredients:	Budesonide; Formoterol fumarate; Glycopyrrolate
Dosage Form:	Aerosol, metered
Route:	Inhalation
Strength:	0.16 mg/inh; 0.0048 mg/inh; 0.009 mg/inh
Recommended Studies:	Two options: (1) seven in vitro bioequivalence studies*, one comparative characterization study, and two in vivo bioequivalence studies with pharmacokinetic endpoints, or (2) five in vitro bioequivalence studies, one comparative characterization study, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

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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 reference standard (RS) that may affect local or systemic availability (e.g., qualitatively (Q1)/quantitatively (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 Model(s) for regional drug delivery***
  - Device similarity to the reference listed drug (RLD)

Suspension MDI PSGs Incorporating Alternative BE Approaches

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Option 2 BE Approach

- **Formulation**
  - *No recommendations provided (e.g., T product formulation can 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 asthma subjects*
- **Additional Information**
  - *Optional Computational Model(s) for regional drug delivery*
  - Device similarity to the reference listed drug (RLD)

Implementing the Agency's Current Thinking for DPIs

RELENZA
Zanamivir Inhalation Powder

- *Capsule-based DPI*
- **Indication**:
  - The treatment of acute, uncomplicated influenza type A and B infections in patients 7 years and older who have been symptomatic for no more than 2 days.
  - Prophylaxis of influenza in patients aged 5 years and older.
- **Formulation**: Zanamivir and lactose monohydrate

BRONCHITOL
Mannitol Inhalation Powder

- *Capsule-based DPI*
- **Indication**:
  - Add-on maintenance therapy to improve pulmonary function in adult patients 18 years of age and older with cystic fibrosis.
- **Formulation**: Mannitol (no inactive ingredients)

DPI PSGs Incorporating Alternative BE Approaches

Draft DPI PSG (Feb 2024)

Active Ingredient:	Zanamivir
Dosage Form:	Powder
Route:	Inhalation
Strength:	5 mg
Recommended Studies:	Three in vitro bioequivalence studies and two comparative characterization studies

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- ***No in vivo PK BE study recommended.***
- ***For this DPI, systemic exposure equivalence supported by other included BE studies.***

BE Approach

- **Formulation**
  - The test (T) product should contain ***no difference in inactive ingredients or other aspects of the formulation*** relative to the reference standard (RS) that may affect local or systemic availability (e.g., qualitatively (Q1)/quantitatively (Q2) formulation sameness)
- **In Vitro BE Studies**
  - SAC, APSD
  - ***rAPSD***
- **Comparative Characterization Studies**
  - ***Polymorphic Form of the Drug Substance***
  - ***Particle Morphology of the Emitted Dose***
- **Additional Information**
  - ***Optional Computational Model(s) for regional drug delivery***
  - Device similarity to the reference listed drug (RLD)

DPI PSGs Incorporating Alternative BE Approaches

Draft DPI PSG (Feb 2024)

Active Ingredient:	Mannitol
Dosage Form:	Powder
Route:	Inhalation
Strength:	40 mg
Recommended Studies:	Three in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative characterization study 18

- ***No in vivo PK BE study (without charcoal block) is recommended.***
  - ***For this DPI, systemic exposure equivalence supported by other included BE studies.***

For this DPI:

- ***PK BE study with Charcoal Block***
  - ***Aids in evaluating local drug delivery.***

BE Approach

- **Formulation**
  - The test (T) product should contain ***no difference in formulation*** relative to the reference standard (RS) that may affect local or systemic availability of the active ingredient.
- **In Vitro BE Studies**
  - SAC, APSD
  - ***rAPSD***
- **Comparative Characterization Studies**
  - ***Particle Morphology of the Emitted Dose***
- **In Vivo Studies**
  - ***In Vivo PK BE study with Charcoal Block***
- **Additional Information**
  - ***Optional Computational Model(s) for regional drug delivery***
  - Device similarity to the reference listed drug (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.

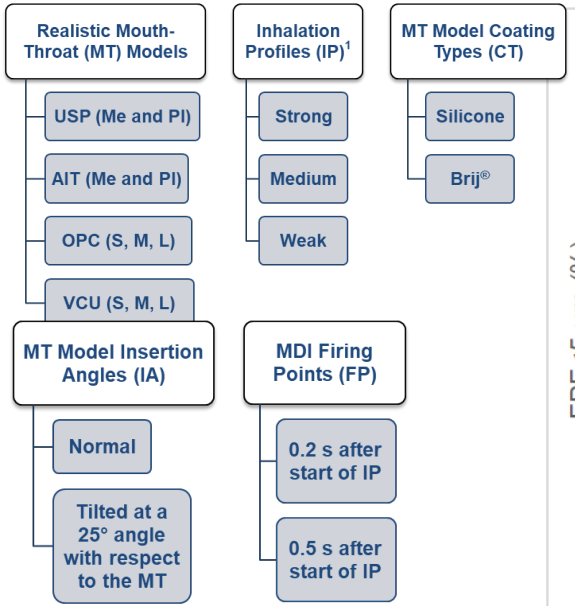


Figure 2: Study design factors evaluated for rAPSD with solution and suspension-based MDIs.[6]

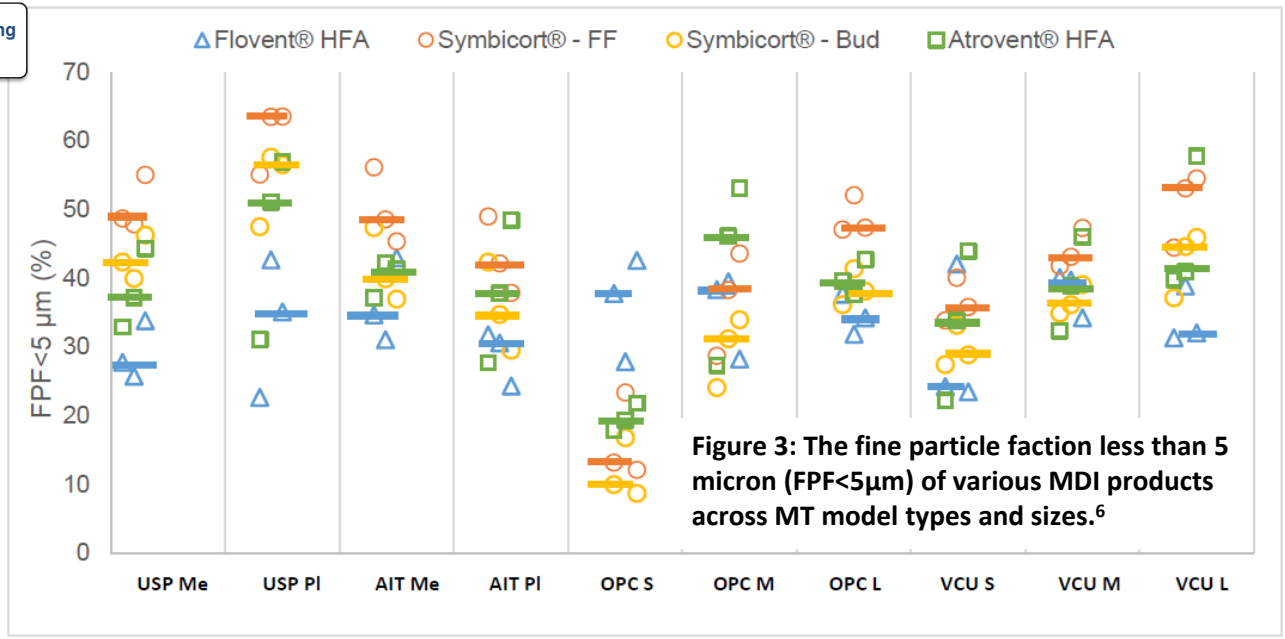
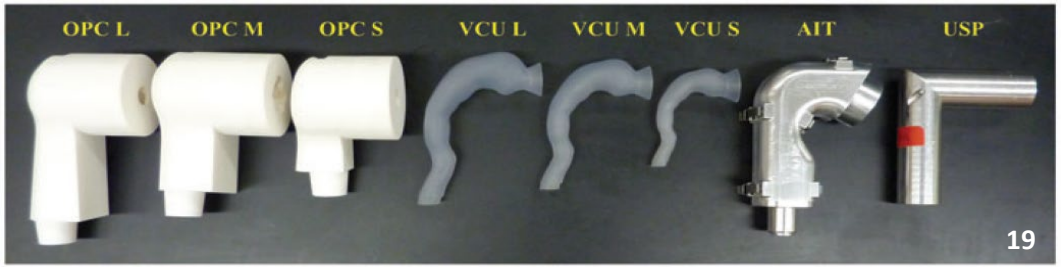


Figure 3: The fine particle faction less than 5 micron (FPF<5µm) of various MDI products across MT model types and sizes.[6]

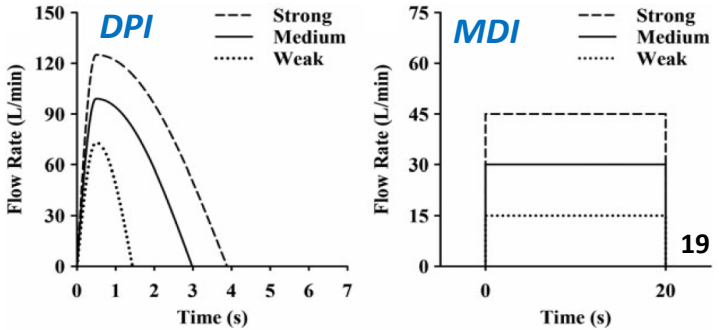
USP: United States Pharmacopeia; AIT: Albert Idealized Throat; OPC: Oropharyngeal Pharmacopeia Consortium; VCU: Virginia Commonwealth University

Realistic APSD Study Design Considerations

Realistic mouth-throat (MT) models



Inhalation profiles (IPs)



- **PSG Recommendations:**
  - **Beginning** lifestage
  - Include different ***mouth-throat (MT) sizes*** and ***inhalation profiles (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-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

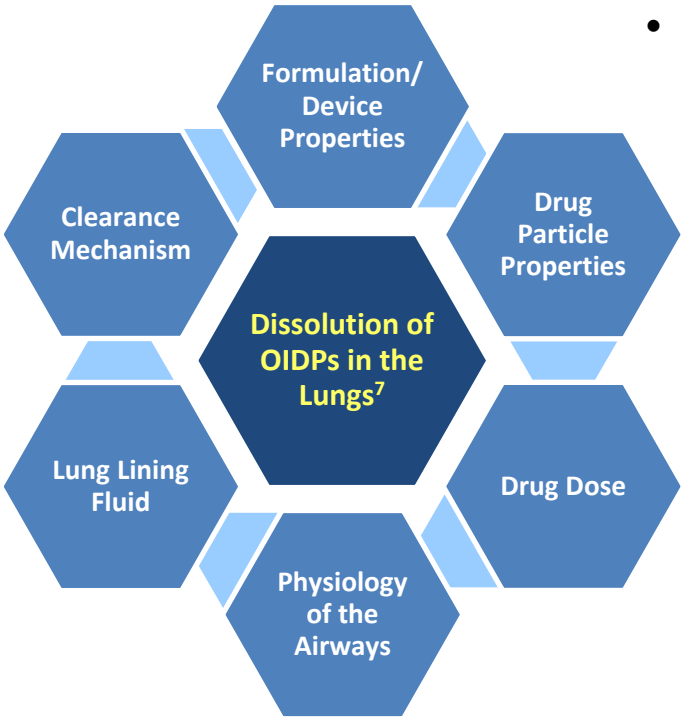


Figure 4: Drug dissolution in the lungs can be impacted by multiple factors.[20]

- **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 ***API-*** (e.g., high/low solubility) and ***product-specific.***

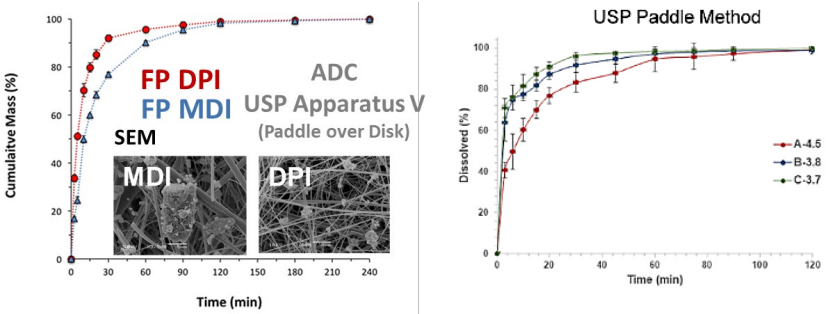


Figure 5: Dissolution of OIDPs can are sensitive to differences in both dosage form (left) and particle size (right).[8,9]

Dissolution Study Design Considerations for OIDPs

Sample Collection

Dissolution Apparatus

Dissolution Media

Method Validation

Assessment

- **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***).

In Vivo Charcoal Block PK BE Study Considerations

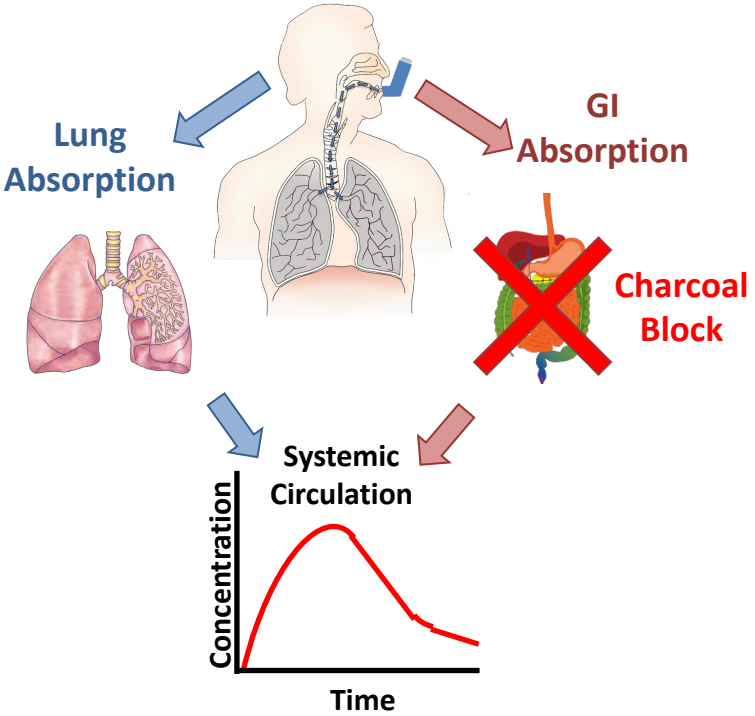


Figure 6: Drug absorption into the systemic circulation following dosing with certain OIDPs can occur through both lung absorption as well as gastrointestinal (GI) absorption. Dosing with charcoal can block GI absorption.

- 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 its 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

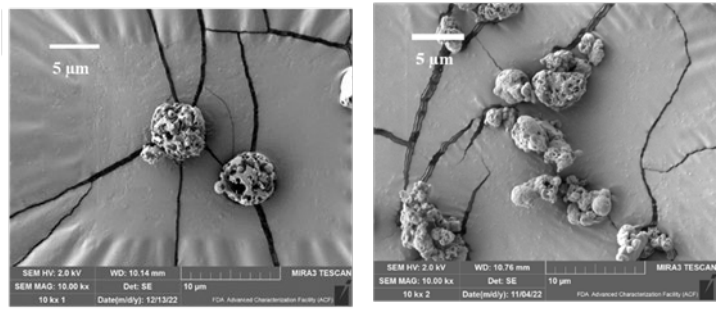
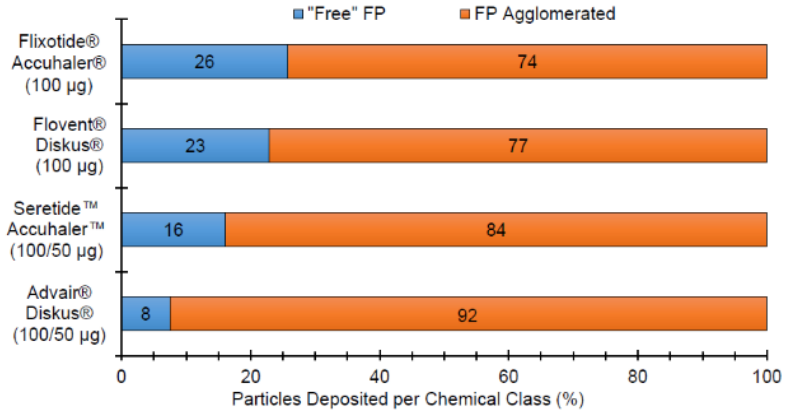


Figure 7: SEM images of phospholipid porous particles found in a marketed DPI (left) and MDI (right) [21]

- ***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.



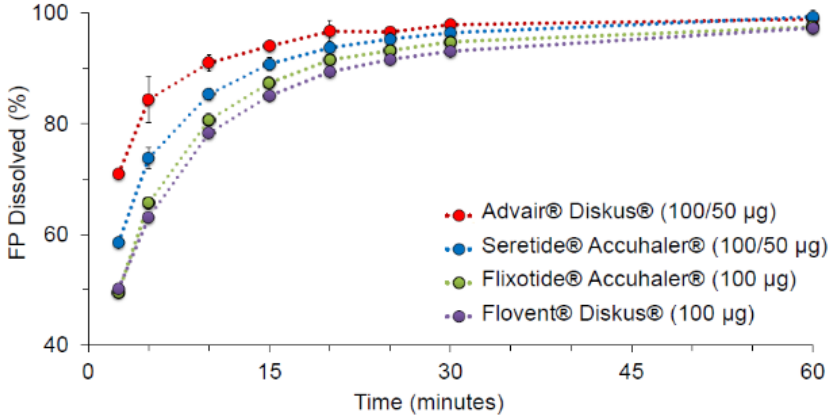


Figure 8: Microstructural differences in the deposited particle agglomerates (left) may be one potential contributing factor to performance differences, such as with dissolution performance (right).[1]

Comparative Characterization Study Considerations

- **PSG Recommendations:**
  - A minimum of ***three batches*** of the T and RS product should be testing 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.

Optional Computational Model(s) as Supportive Studies

- ***In silico computational models*** can provide support for a wide array of questions impacting both **drug development** and assessment of **performance**.
- Various in silico models (e.g., ***regional deposition modeling, CFD, PBPK***) are available and can serve **different purposes**.

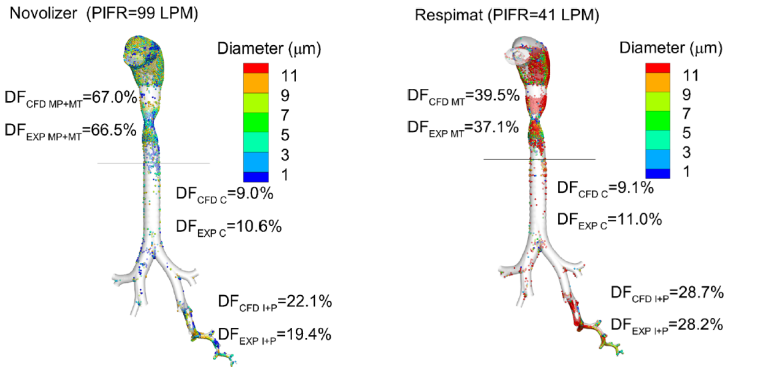
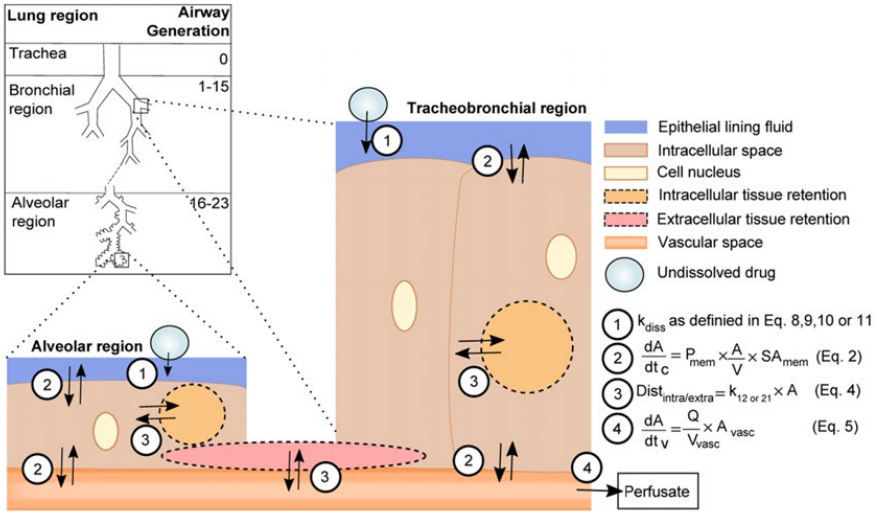


Figure 9: Computation fluid dynamic (CFD) models (left) and physiologically based PK (PBPK) models (right) are two samples of computation models that can support BE assessments as well as drug development.[22,23]



Optional Computational Model(s) as Supportive Studies

- **PSG Recommendations:**
  - ***Purpose***
    - Impact of product factors on regional drug delivery to establish biorelevant BE limits for BE studies (e.g., rAPSD, plume geometry).
    - Assess regional lung deposition BE via virtual simulations.
  - Model ***purpose*** should be **well stated.**
    - Example: CFD or semiempirical model to predict central and peripheral lung deposition
    - Example: PBPK models useful if drug absorption is not expected to be rapid, such that regional deposition may not be considered as a surrogate for regional lung delivery.
  - Model ***credibility*** and ***validation*** should be established.
  - Model ***verification*** is needed to establish **credibility.**
  - Model ***validation acceptance criteria*** and the ***statistical analysis methods*** for virtual BE studies should be **defined prior to testing** and be **justified.**

Full Details: PSG on *Formoterol Fumarate; Glycopyrrolate Inhalation Aerosol Metered* (NDA 208294).

Conclusions

- 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 and DPIs.***
- 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.

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