

# **FDA Recommendations for Alternative Bioequivalence Approaches: Design and Rationale for In Vitro and In Vivo Studies**

**Respiratory Drug Delivery (RDD) 2024**

May 7, 2024

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# Disclaimer



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# Outline

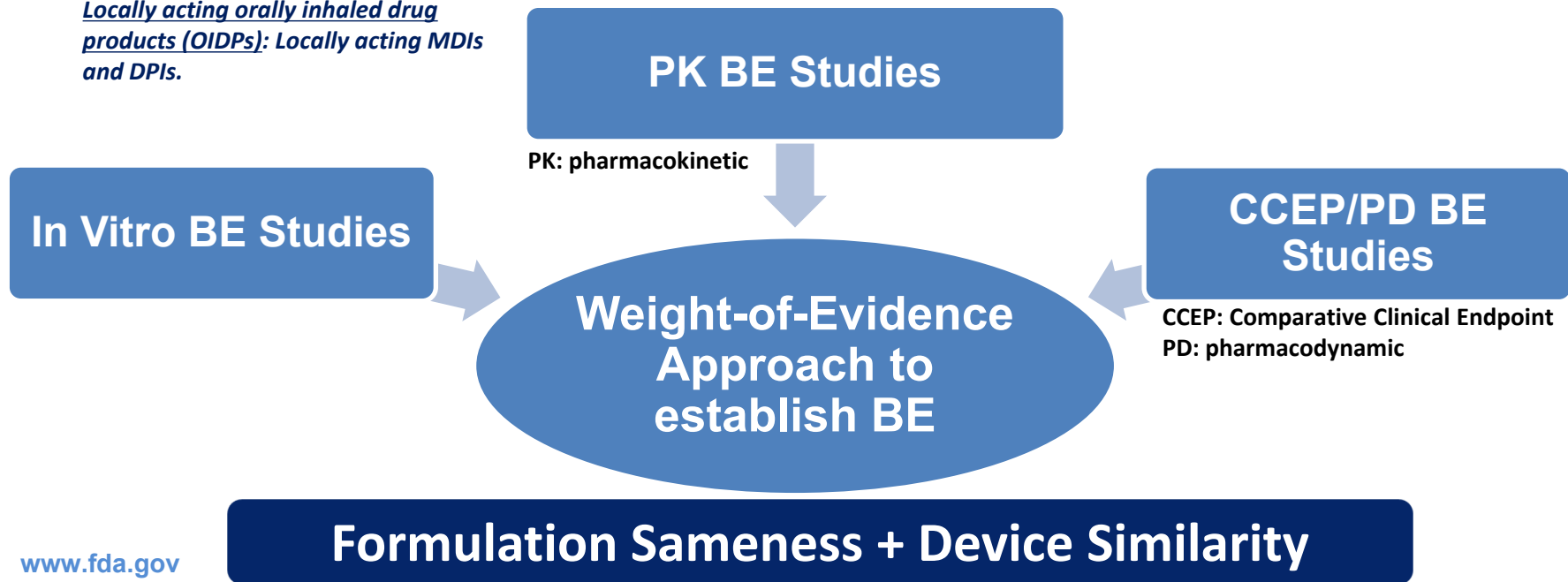
- Brief overview of the challenges with *conducting comparative clinical endpoint (CCEP) bioequivalence (BE) studies* for orally inhaled drug products (OIDPs).
- Exploring the available tools, supportive FDA research, and external input for developing *alternative BE approaches*.
- Recently developed 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.

# FDA's Historical Approach for Establishment of 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 MDIs and DPIs.



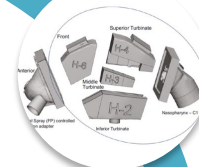
# The Challenges with CCEP BE Studies



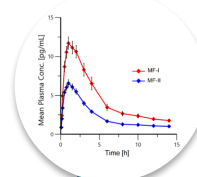
- CCEP BE studies can pose several **challenges** for generic applicants developing an MDI or DPI.
  - **Higher variability** → *lower accuracy and reproducibility*
  - **Flat exposure-response** → *lower sensitivity*
- Ultimately, these challenges necessitate using **large numbers** of patients often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

CCEP BE  
Studies

Alternative  
BE  
Approaches



In Vitro  
Methods

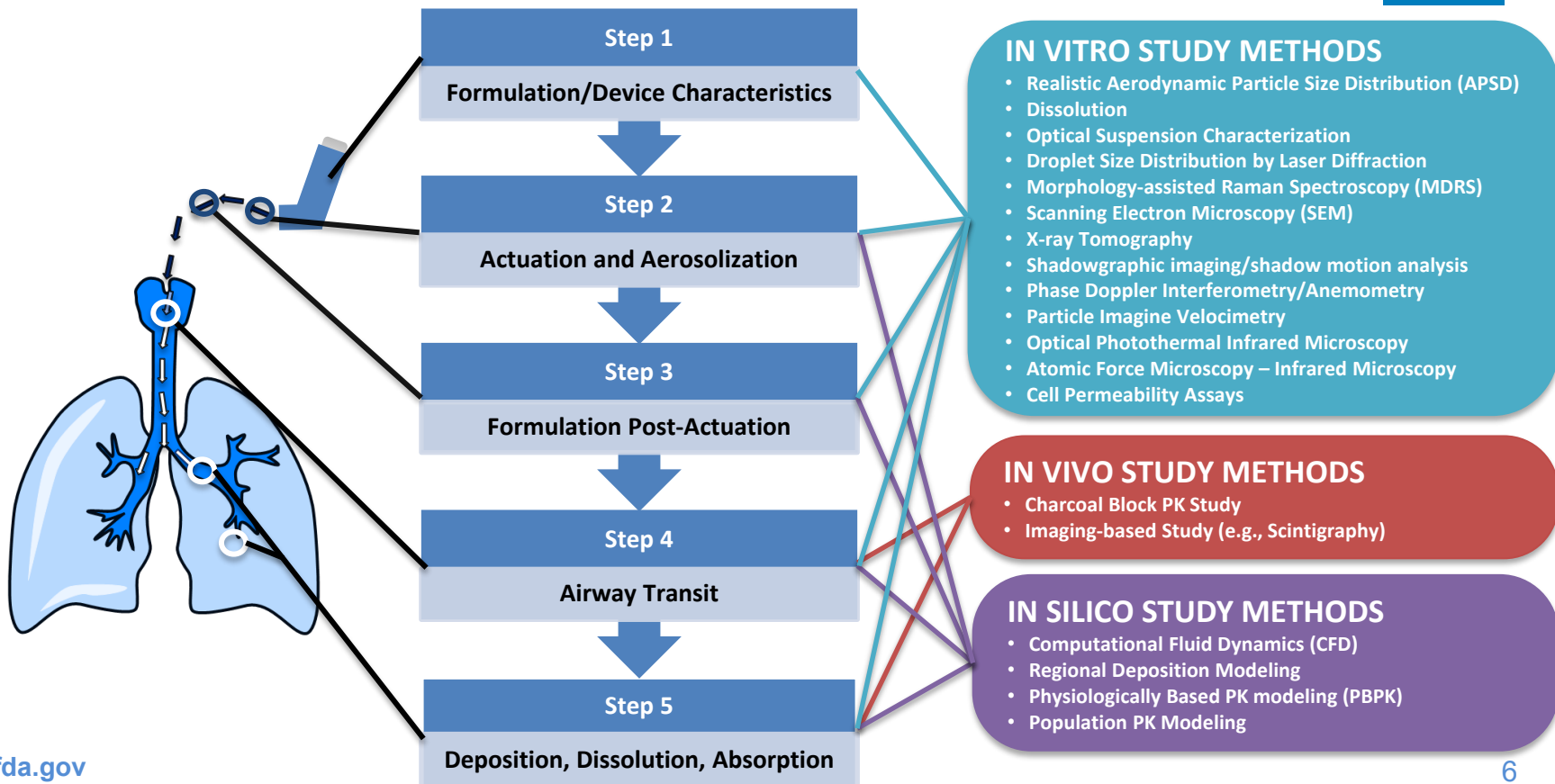


In Vivo  
Methods



In Silico  
Methods

# Potential Methods for Assessing Contributing Factors to Local Drug Delivery



# ORS Research Activities for ODPs

Formulation

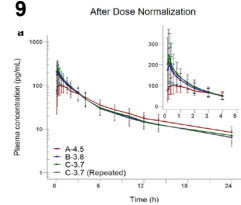
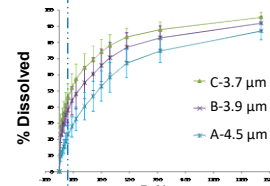
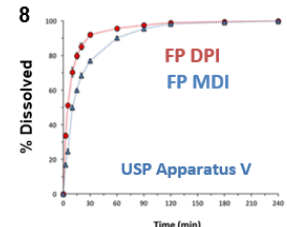
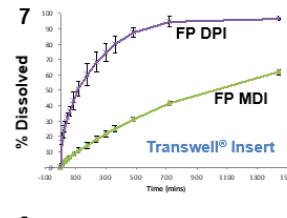
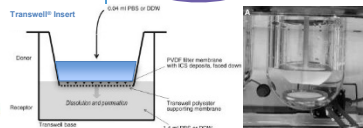
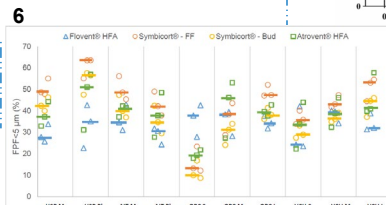
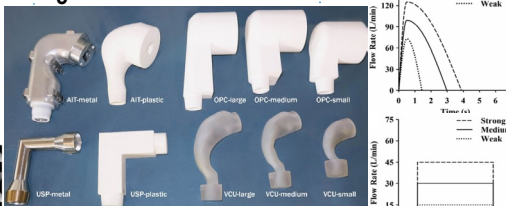
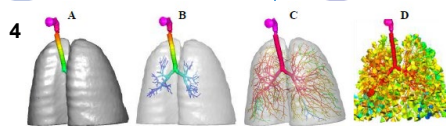
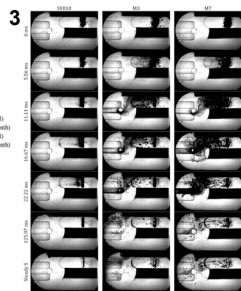
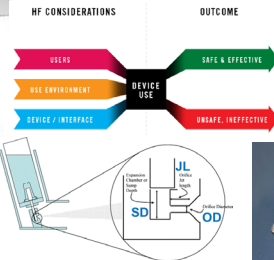
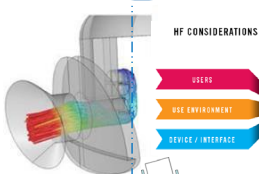
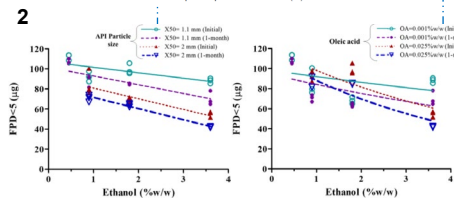
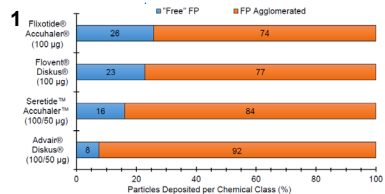
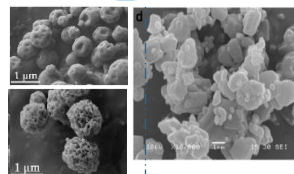
Device

User Interface

Regional Deposition

Dissolution

Absorption



# 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

## More Predictive APSD Testing (representative mouth-throat models and breathing profiles)

- Understand impact of patient variability

Transit  
through the  
airways;  
Deposition,  
Dissolution,  
Absorption

## Dissolution

- Understanding how drug(s) dissolves at the site of action for absorption once deposited

## Quantitative Methods and Modeling (e.g., PBPK, CFD studies)

- IVIVCs to bridge gap between in vitro product performance and regional drug deposition

Methods for  
further  
support

## Alternative PK BE Studies

- Understanding how PK studies may correlate to local deposition

Initial Applicability:  
Solution-based MDIs

Framework for  
alternative BE  
approach for ODPs

Applicable to  
suspension-based  
MDIs and DPIs?



# External Input Informs FDA Thinking on Alternative BE Approaches for OIDPs



**Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products**

**April 20-21, 2023**  
**8:30 AM – 5:30 PM**

In-Person and Virtual Options to Attend

The purpose of this two-day orally inhaled drug products (OIDP) workshop is to discuss the current scientific and regulatory perspectives for using in vivo, in vitro, and in silico studies as alternatives to comparative clinical endpoint (CCEP) and pharmacodynamic (PD) bioequivalence (BE) studies, and to explore potential designs for alternative BE approaches that can address the particular challenges associated with establishing local drug delivery equivalence for suspension-based metered dose inhalers (MDIs) and dry powder inhalers (DPIs).

**Workshop Topics:**

- ✓ Reviewing successes with the use of CCEP and PD BE studies to establish BE for locally acting OIDPs, and discussing relevant challenges
- ✓ Evaluating alternative BE approaches that utilize in vitro, in vivo, and in silico studies, instead of CCEP and PD BE studies, and discussing relevant technical and practical issues when used with different OIDPs
- ✓ Discussing the integration of multiple alternative in vitro, in vivo, and in silico studies to form cohesive alternative BE approaches in lieu of CCEP or PD BE studies for MDIs and DPIs



**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 ODPs



- 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**

## 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

# Implementing the Agency's Current Thinking for Suspension MDIs



## BEVESPI AEROSPHERE

Formoterol Fumarate; Glycopyrrolate  
Metered Inhalation Aerosol

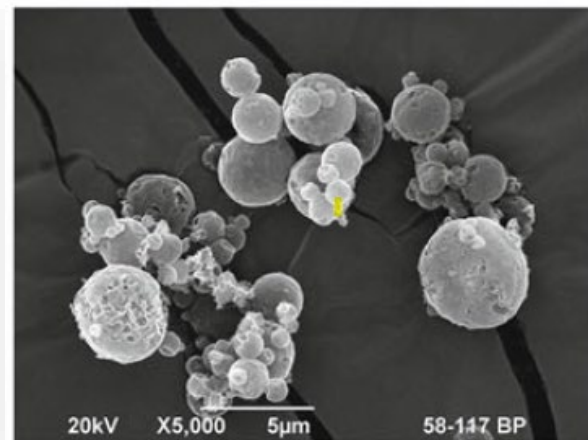


## BREZTRI AEROSPHERE

Budesonide; Formoterol Fumarate;  
Glycopyrrolate Metered Inhalation Aerosol



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



An example of phospholipid-based porous particles utilized in several MDI products.<sup>12</sup>

- **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

# Suspension MDI PSGs

## Incorporating Alternative BE Approaches

### Draft Suspension MDI PSGs (Feb 2024)

<b>Active Ingredients:</b>	Formoterol fumarate; Glycopyrrolate
<b>Dosage Form:</b>	Aerosol, metered
<b>Route:</b>	Inhalation
<b>Strength:</b>	0.0048 mg/inh; 0.0090 mg/inh
<b>Recommended Studies:</b>	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
<b>13</b>	

<b>Active Ingredients:</b>	Budesonide; Formoterol fumarate; Glycopyrrolate
<b>Dosage Form:</b>	Aerosol, metered
<b>Route:</b>	Inhalation
<b>Strength:</b>	0.16 mg/inh; 0.0048 mg/inh; 0.009 mg/inh
<b>Recommended Studies:</b>	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
<b>14</b>	

### 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

# Suspension MDI PSGs

## Incorporating Alternative BE Approaches

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<b>14</b>	

### 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



# Implementing the Agency's Current Thinking for DPIs



## RELENZA Zanamivir Inhalation Powder



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- **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



16

- **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 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
  - *rAPSD*
- **Comparative Characterization Studies**
  - *Polymorphic Form of the Drug Substance*
  - *Particle Morphology of the Emitted Dose*
- **Additional Information**
  - Optional Computational Modeling study
  - Device similarity to the 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

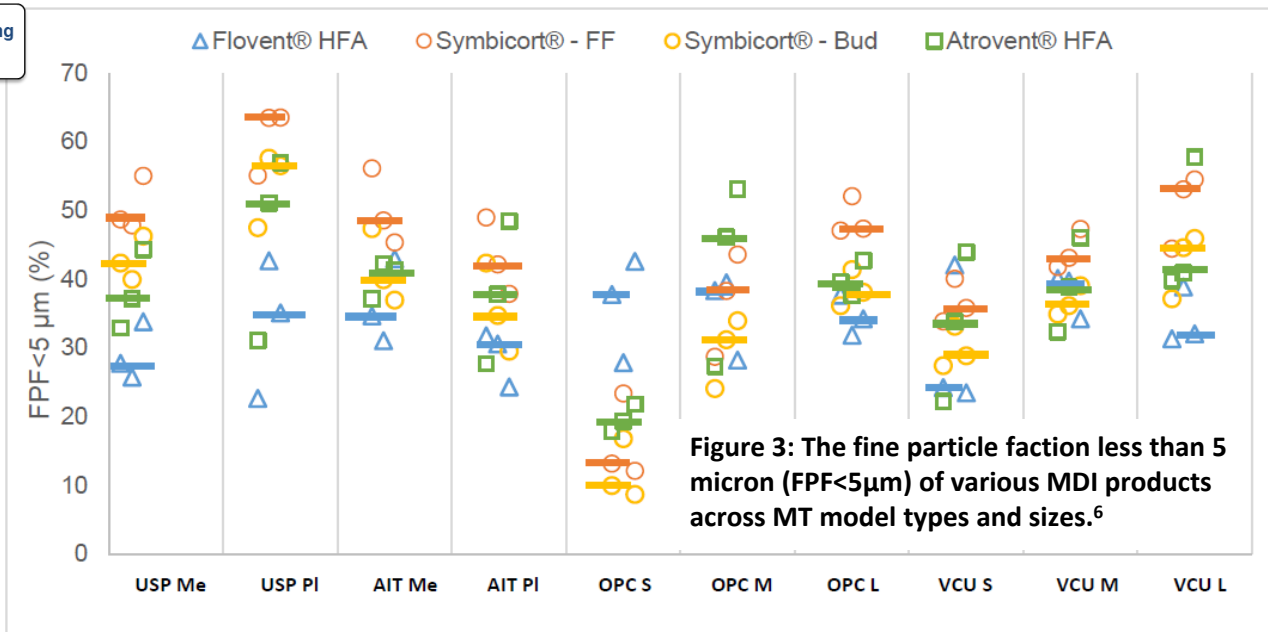
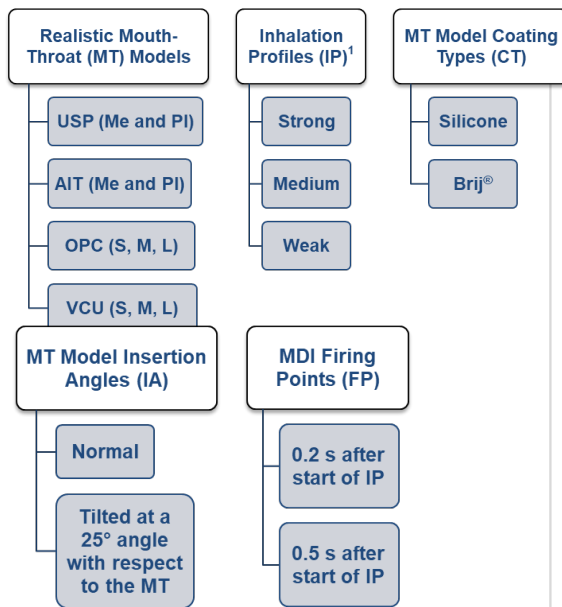
- **Formulation**
  - The T product should contain ***no difference in formulation*** relative to the RS that may affect local or systemic availability of the active ingredient.
- **In Vitro BE Studies**
  - SAC, APSD
  - ***rAPSD***
- **Comparative Characterization Studies**
  - ***Particle Morphology of the Emitted Dose***
- **In Vivo Studies**
  - ***In Vivo PK BE study with Charcoal Block***
- **Additional Information**
  - Optional Computational 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.

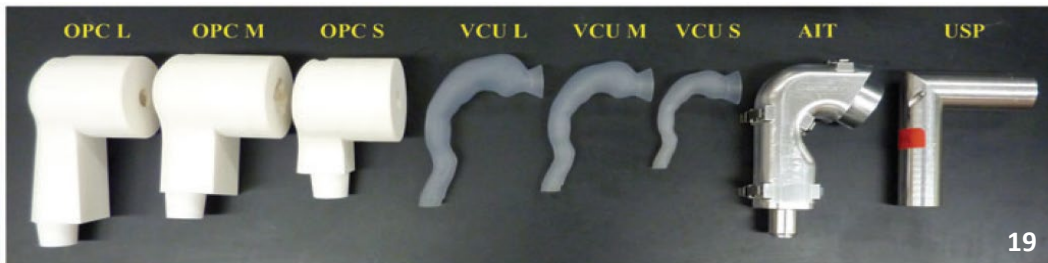


Study design factors evaluated for rAPSD with solution and suspension-based MDIs.<sup>6</sup>

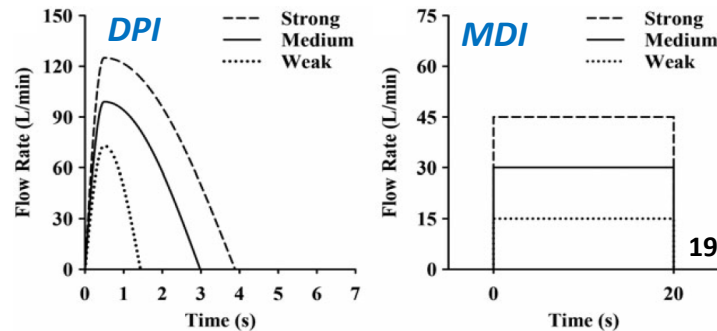
USP: United States Pharmacopeia; AIT: Albert Idealized Throat; OPC: Oropharyngeal Pharmacopeia Consortium; VCU: Virginia Commonwealth University

# Realistic APSD Study Design Considerations

## Realistic mouth-throat (MT) models

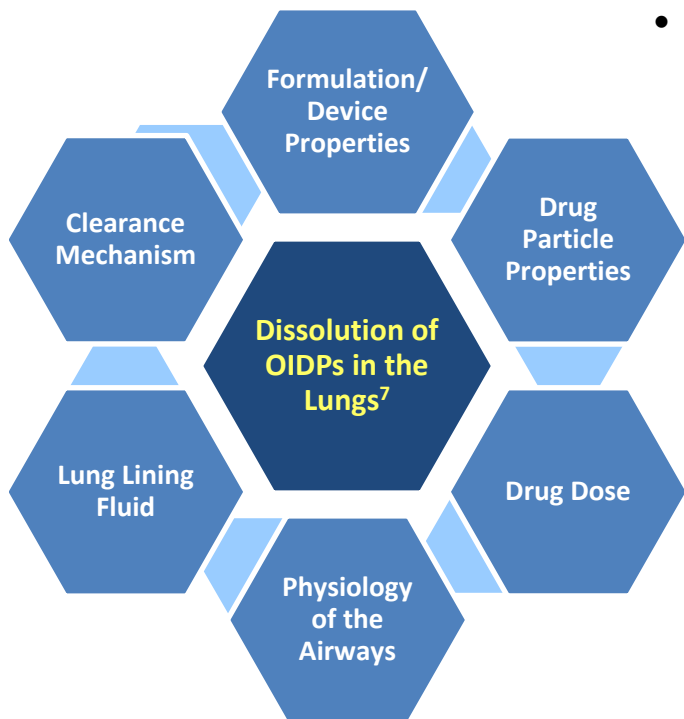


## Inhalation profiles (IPs)



- **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 ODPs

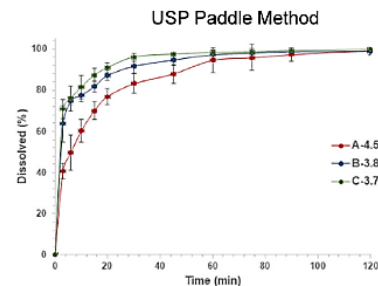
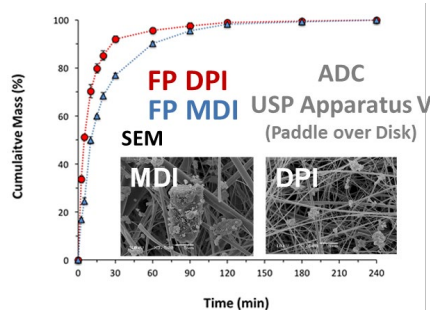


Drug dissolution in the lungs can be impacted by multiple factors.<sup>20</sup>

[www.fda.gov](http://www.fda.gov)

- 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 ODPs are sensitive to differences in both dosage form (left) and particle size (right).<sup>8,9</sup>

# Dissolution Study Design Considerations for ODPs



Sample Collection

Dissolution Apparatus

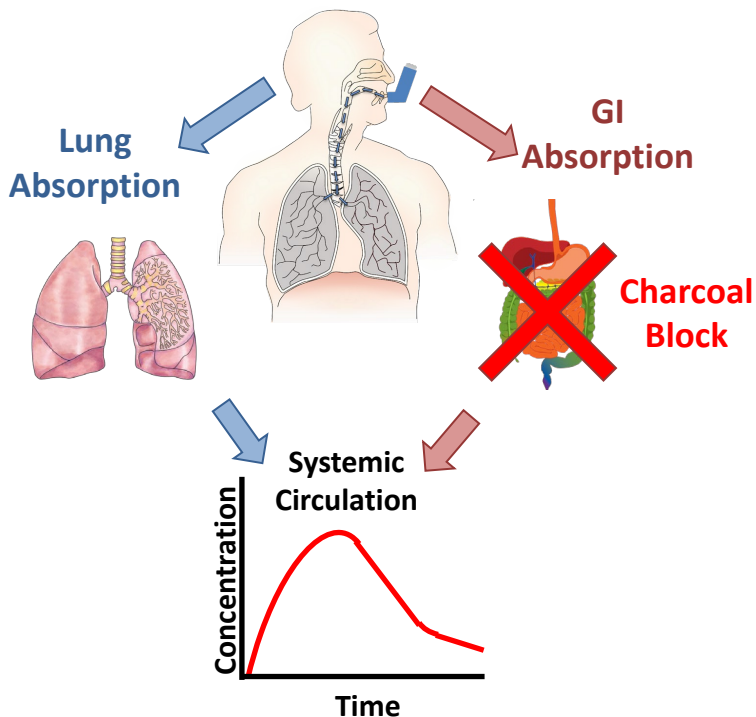
Dissolution Media

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



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

- For ODPs, 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.

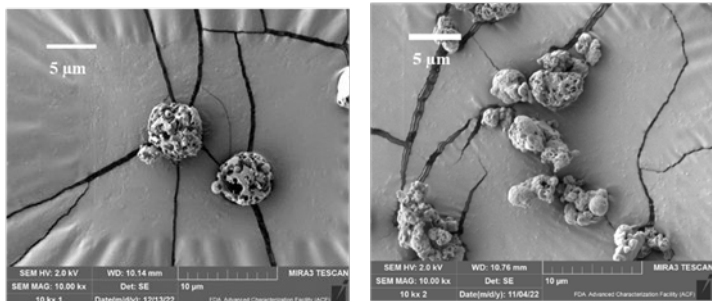
# In Vivo Charcoal Block PK BE Study Considerations



- PSG Recommendations:

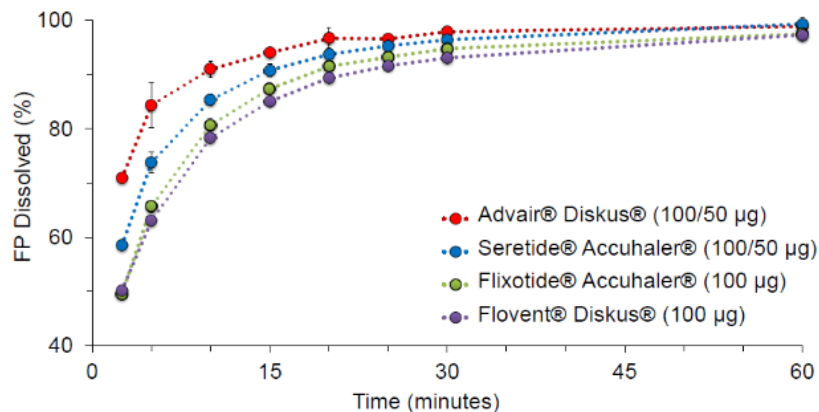
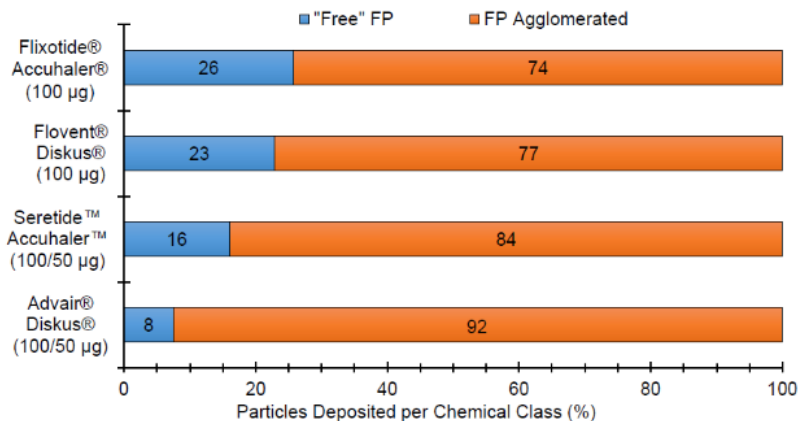
- Similar to PK BE study in many aspects.
  - **Healthy** adult male and female subjects.
  - **Minimum number of inhalations** to sufficiently characterize the PK profile with a sensitive analytical method.
  - Dose administration should follow the approved labeling instructions.
  - **Bio-IND** may 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) <sup>21</sup>

- **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).<sup>1</sup>



# 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.

# Conclusions



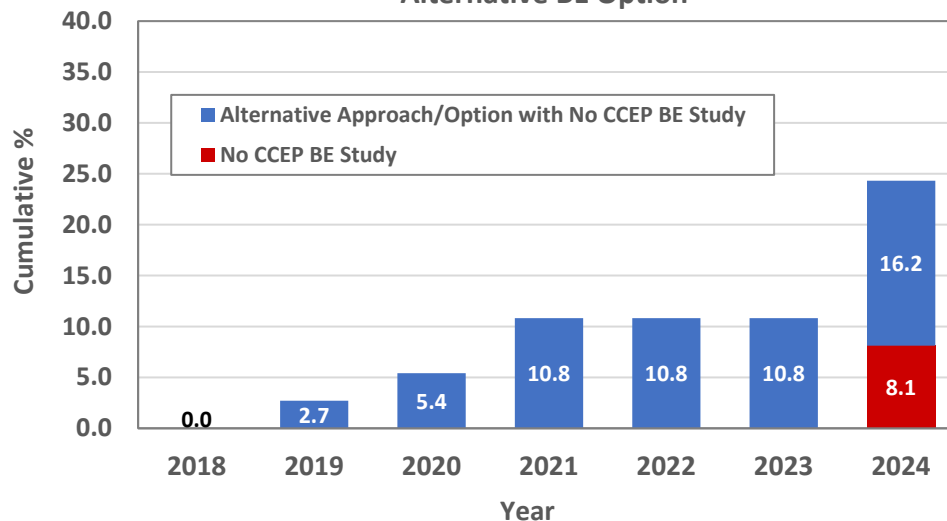
- The challenges with conducting *CCEP BE studies* can lead to higher costs and longer drug development timelines for generic developers of ODPs.
- To address these challenges, FDA has explored *in vitro, in vivo, and in silico study designs* through GDUFA-funded research initiatives to identify *alternative 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 ODPs in 2023, FDA has utilized the input received from industry and academic attendees to aid the development of several *PSGs for DPLs and 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.

# PSGs of Locally Acting MDIs and DPIs with No Recommended CCEP BE study or Alternative BE Option Available



- Since 2018, FDA has increased the percentage of available PSGs for locally acting MDIs and DPIs
  - Recommend **alternative approaches** to CCEP BE studies
  - **Do not recommend** the CCEP BE study
- **2018:**
  - **0 %** of available PSGs had alternative BE approaches to a CCEP BE study (i.e., a CCEP BE study recommended in every case)
- **2019:**
  - **First alternative BE approach/option** available
- **2024:**
  - **8.1%** - PSGs with no recommended CCEP BE study
  - **16.2%** - alternative approach/option available
  - Total → **24.3%**

Cumulative Percentages of PSG for Locally Acting MDIs and DPIs, with No CCEP BE Study and/or Has an Available Alternative BE Option



# Acknowledgements

- **FDA/CDER/OGD/ORS**
  - Bryan Newman
  - Liangfeng Han
  - Anubhav Kaviratna
  - Ross Walenga
  - Steven Chopski
  - Andrew Babiskin
  - Darby Kozak
  - Markham Luke
  - Liang Zhao
  - Lei Zhang
  - Robert Lionberger
- **FDA/CDER/OGD/OB**
  - Tian Ma
  - Zhen Xu
  - Ke Ren
  - Eunjung Park
  - Bing Li
- **FDA/CDER/OGD/OSCE**
  - Kimberly Witzmann
  - William Chong
  - Christina Streets
  - Margarita Tossa
- **FDA/CDER/OPQAI**
  - Nashwa El-Gendy
  - Dhaval Gaglani
- **External Research Collaborators**
  - Günther Hochhaus
  - Jürgen Bulitta
  - Marten Svensson
  - Michael Hindle
  - Jagdeep Shur
  - Robert Price
  - Masahiro Sakagami
  - Hak-Kim Chan
  - Agisilaos Kourmatzis
  - Narender Singh
- **FDA/CDER/OPQ/OPQR**
  - Changning Guo

# Questions?

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# 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.

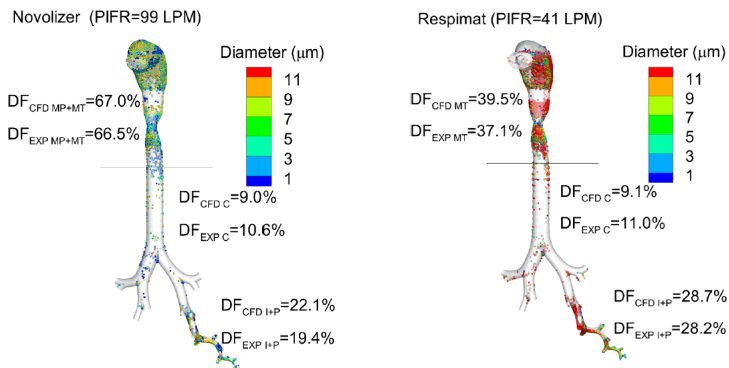
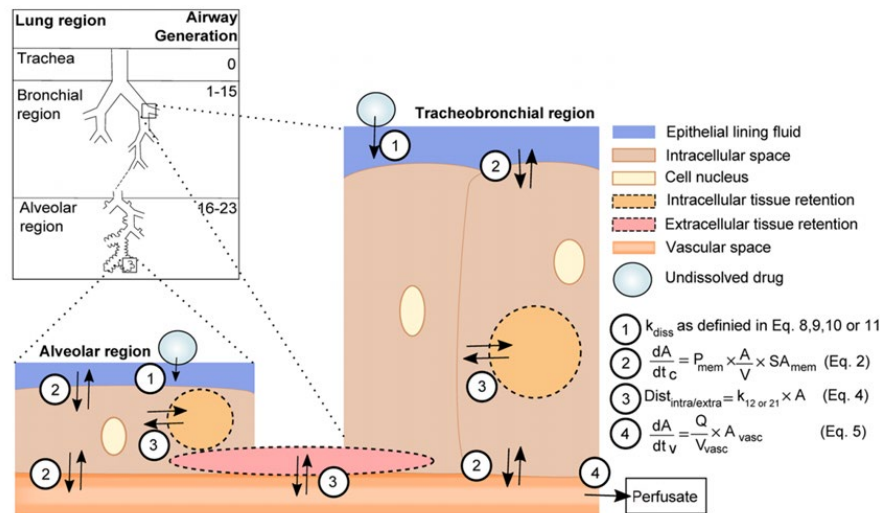


Figure 9: Computation fluid dynamic (CFD) models (left) and physiologically based PK (PBPK) models (right) are two samples of computation models that can support BE assessments as well as drug development.<sup>22,23</sup>



# 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).