FDA's Option-Based BE Approach Recommendations for Locally Acting Metered Dose Inhalers and Dry Powder Inhalers

10th Pulmonary Drug Delivery Conference 2025 (PPD 2025)

June 13, 2025

Elizabeth Bielski, MS PhD
Senior Pharmacologist
Division of Therapeutic Performance-1, Office of Research and Standards
Office of Generic Drugs| CDER | U.S. FDA

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

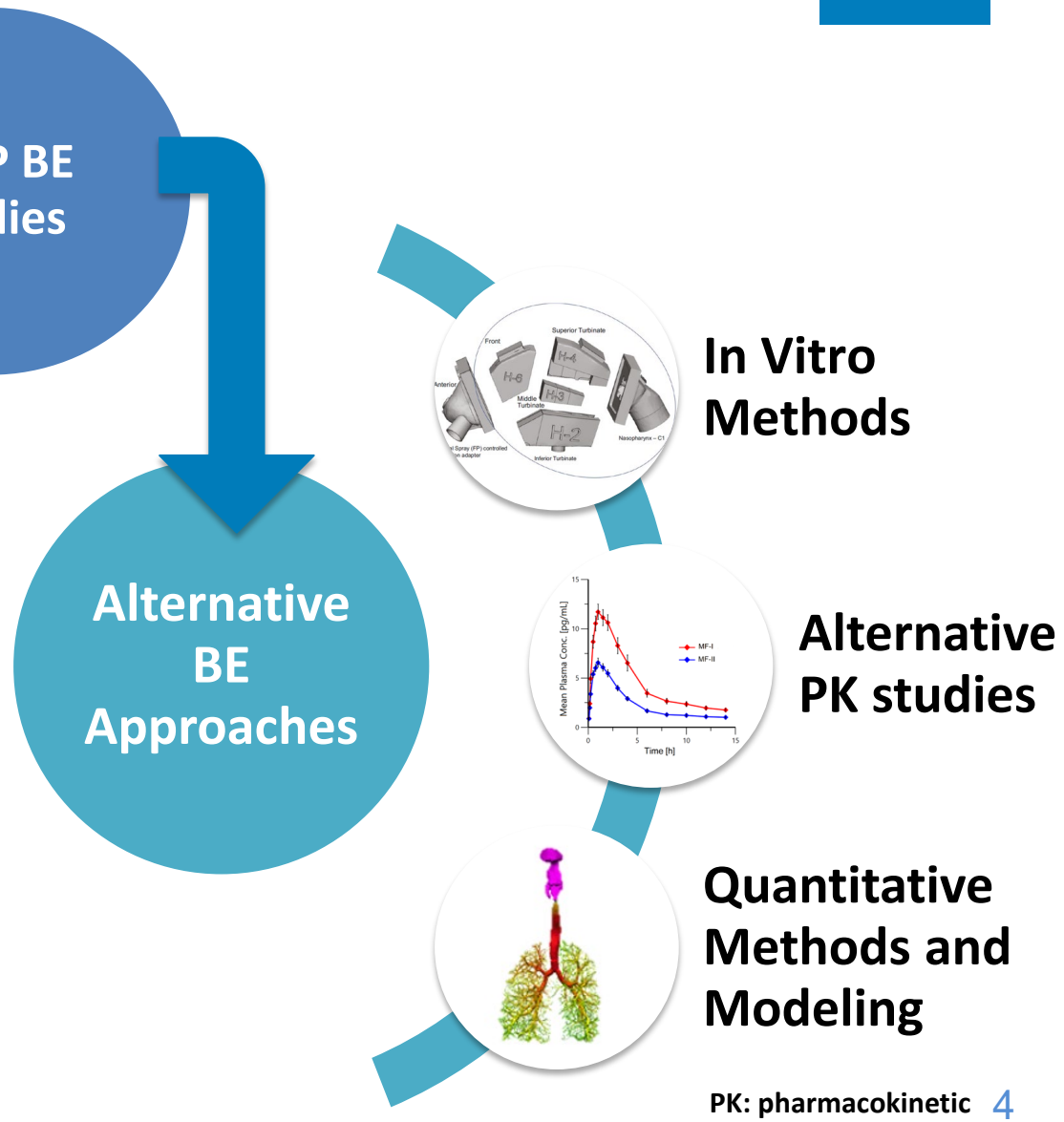
Outline

- 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.***
- An overview of the ***option-based BE approach*** for **OIDPs.**
- Study design considerations for ***formulation sameness*** determination, ***realistic aerodynamic particle size distribution (rAPSD)***, ***dissolution***, ***particle morphology of the emitted dose***, ***charcoal block pharmacokinetic (PK) BE studies***, and ***computational modeling***.
- **Challenges** and **future directions** for ***OIDP BE approaches***.
- Conclusions.

The Challenges with CCEP BE Studies

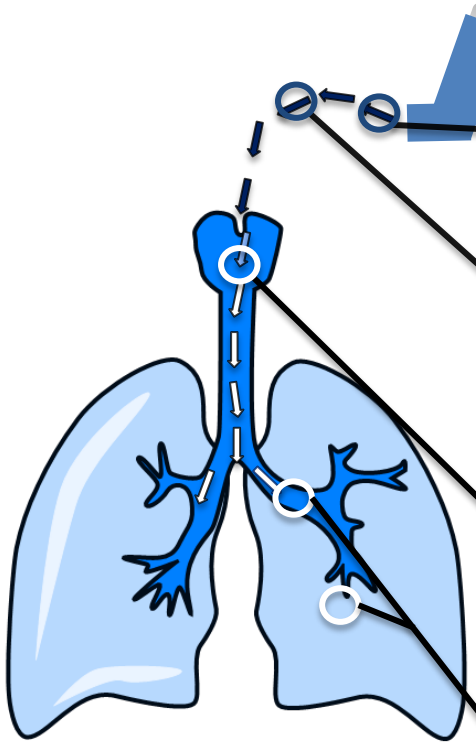
- CCEP BE studies can pose several **challenges** for generic applicants developing an MDI or DPI.
  - *Higher variability* → ***lower accuracy*** *and* ***reproducibility***
  - *Flat exposure-response* → ***lower sensitivity***
- Ultimately, these challenges necessitate using **large numbers** of patients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

MDI: metered dose inhaler; DPI: dry powder inhaler; CCEP: comparative clinical endpoint: BE: bioequivalence



PK: pharmacokinetic

Potential Methods for Assessing Contributing Factors to Local Drug Delivery to the Lungs



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

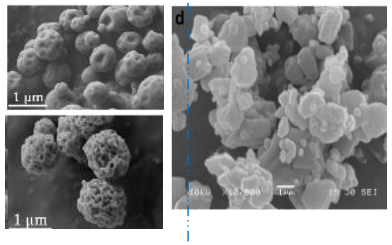
- Charcoal Block Pharmacokinetic (PK) Study
- Imaging – based Study (e.g., Scintigraphy)

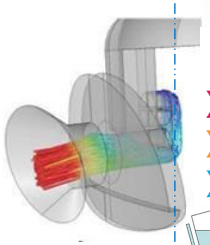
IN SILICO STUDY METHODS

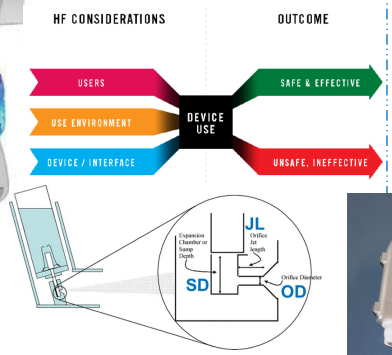
- Computational Fluid Dynamics
- Regional Deposition Modeling
- Physiologically-based PK modeling
- Population PK Modeling

ORS Research Activities for OIDPs

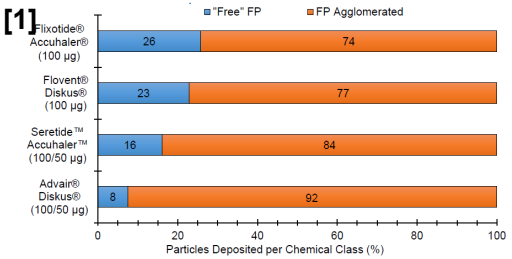
Formulation → Device → User Interface → Regional Deposition → Dissolution → Absorption



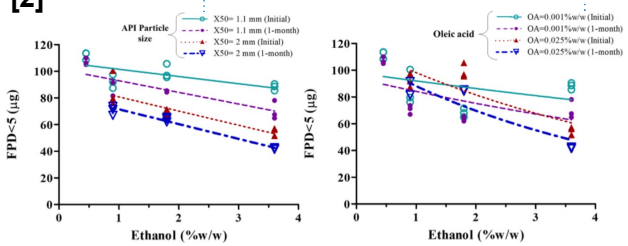




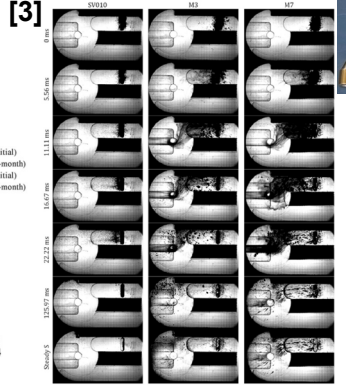
[1]



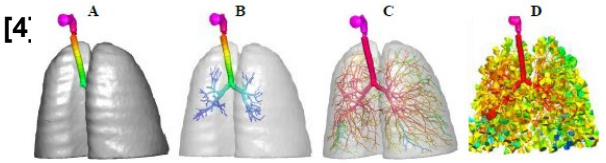
[2]

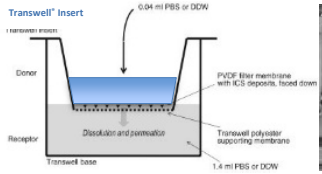


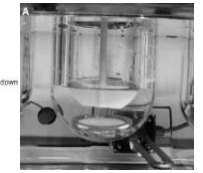
[3]



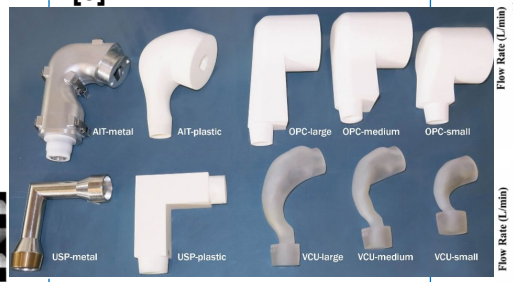
[4]

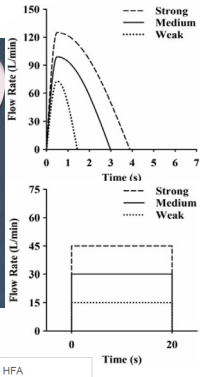




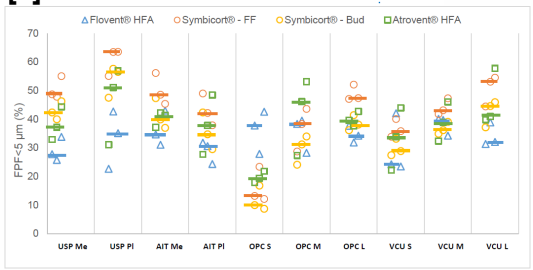


[5]

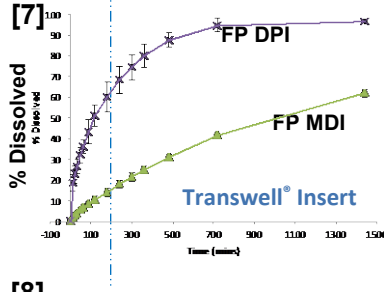




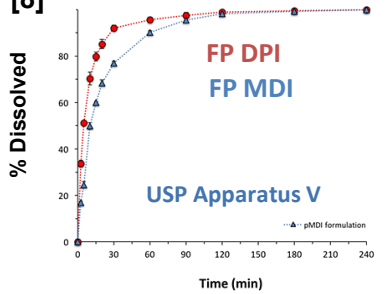
[6]

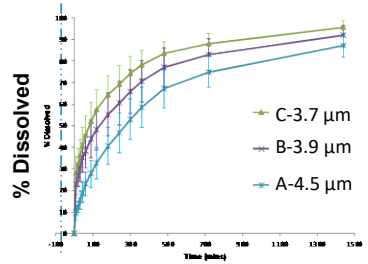


[7]

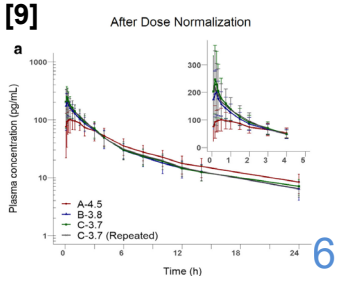


[8]





[9]



Recommendations to Demonstrate BE: MDIs and DPIs

Option 1^

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

Q1: qualitative; Q2: quantitative; RS: reference standard

In Vitro Studies
- SAC, APSD, Spray Pattern, Plume Geometry, Priming/Repriming, rAPSD, Dissolution*

SAC: Single Actuation Content; APSD: aerodynamic particle size distribution; rAPSD: realistic APSD

**When BA of API is dissolution limited*

Comparative Characterization Studies
- Particle Morphology of the Emitted Dose**

***When formulations are more complex*

In Vivo Studies
- PK BE Study, PK BE Study With Charcoal Block***

****When GI absorption of API affects systemic BA*

PK: Pharmacokinetic

Additional Information
- Optional Computational Modeling Study(ies)
- Device Similarity (in design and user interface) to the RLD

Option 2^

Formulation Sameness
- None (e.g., Q1/Q2 or non-Q1/Q2 the same to the RS)

In Vitro Studies
- SAC, APSD, Spray Pattern, Plume Geometry, Priming/Repriming

Comparative Characterization Studies
- Particle Morphology of the Emitted Dose**

***When formulations are more complex*

In Vivo Studies
- PK BE Study, PD/CCEP BE Study

PD: pharmacodynamic; CCEP: Comparative Clinical Endpoint

Additional Information
- Optional Computational Modeling Study(ies)
- Device Similarity (in design and user interface) to the RLD

^ *Refer to the product-specific guidance (PSG) on the MDI or DPI of interest for the specific recommended BE studies.*

Option 1 BE Formulation Recommendations for MDIs and DPIs

Option 1

Formulation Sameness

- The test (T) product should contain no difference in inactive ingredients or other aspects of the formulation relative to the RS that may significantly affect local or systemic availability of the active ingredient (e.g., Q1/Q2 sameness to RS).

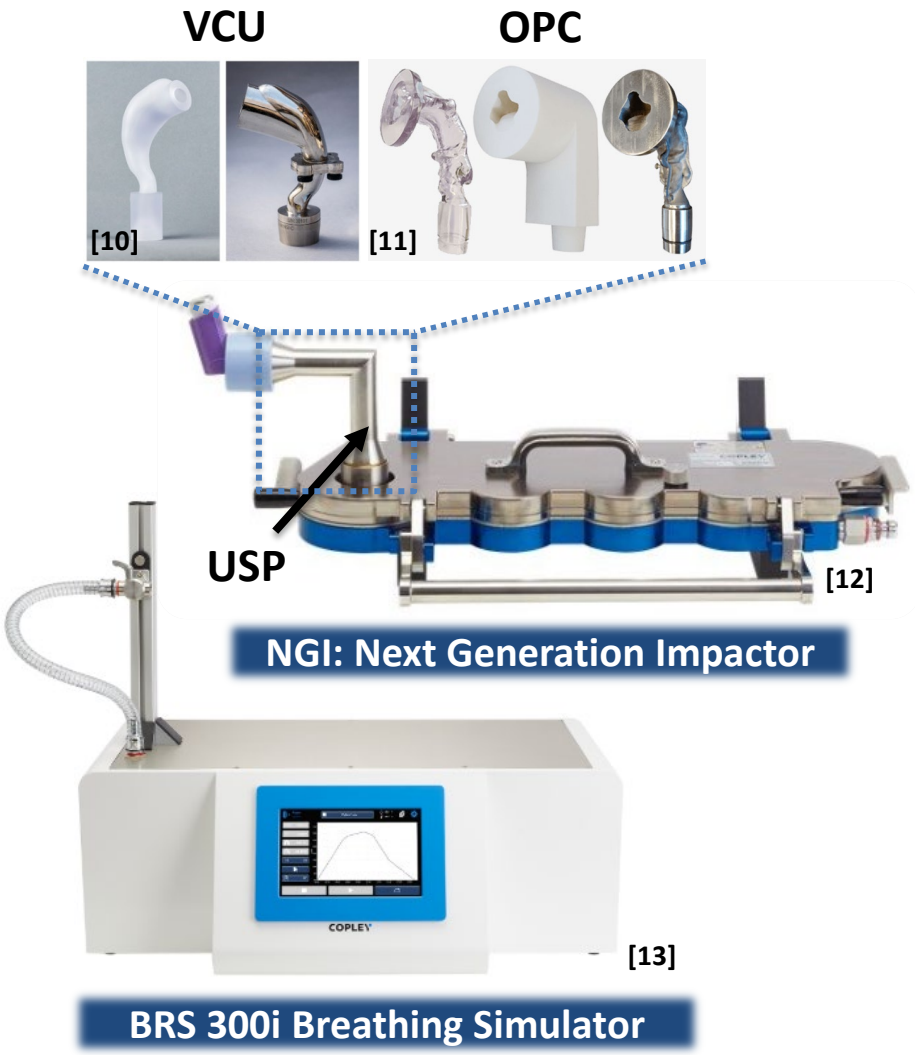
Formulation Sameness

- *Demonstrate Q1/Q2 sameness to RS.*
- *Demonstrate formulation change will not affect local or systemic BA of API.*
  - *Provide justification, which may include, but not limited to formulation characterization data, product development data, comparative characterization studies, and/or scientific literature.*

- *Goal: understand the formulation design space of critical excipients, their ranges, and their potential impact(s) on API bioavailability within the lungs.*
- *Information, data, and/or studies warranted will depend on the formulation changes being proposed.*
- *Ensure formulation difference(s) do not impact desired outcomes in product performance, safety, and efficacy.*
  - *No novel excipients, and consider inactive ingredient maximum daily exposures (MDEs).*

Realistic APSD

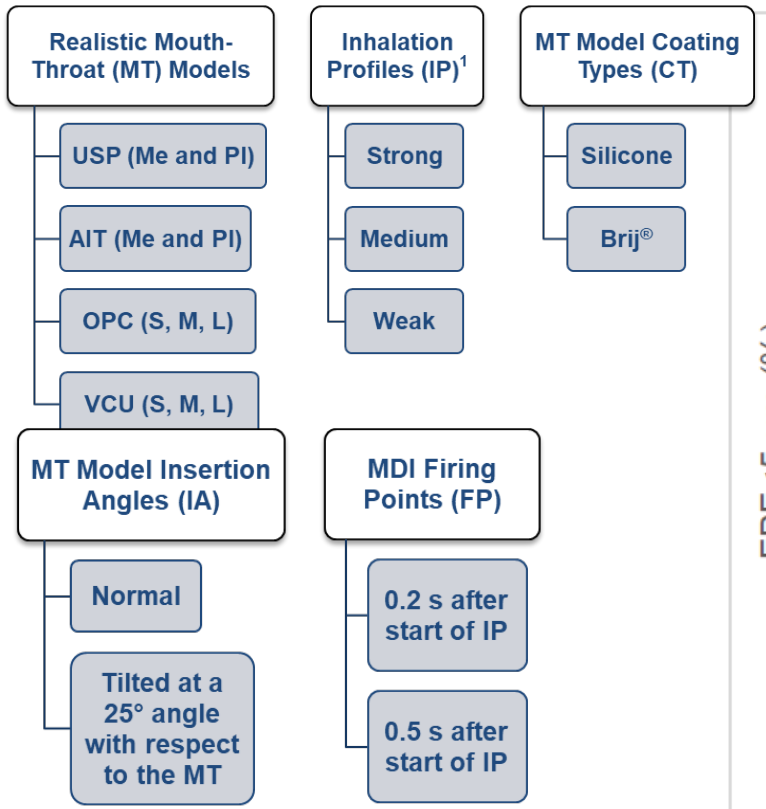
- **Realistic APSD (rAPSD):**
  - Incorporates more ***clinically relevant*** conditions via considering patient factors.
    - **Patient breathing/inhalation profiles (IPs)**
    - Representative ***mouth-throat (MT) models***
  - Understand the ***impact of patient variability*** on aerosol performance.



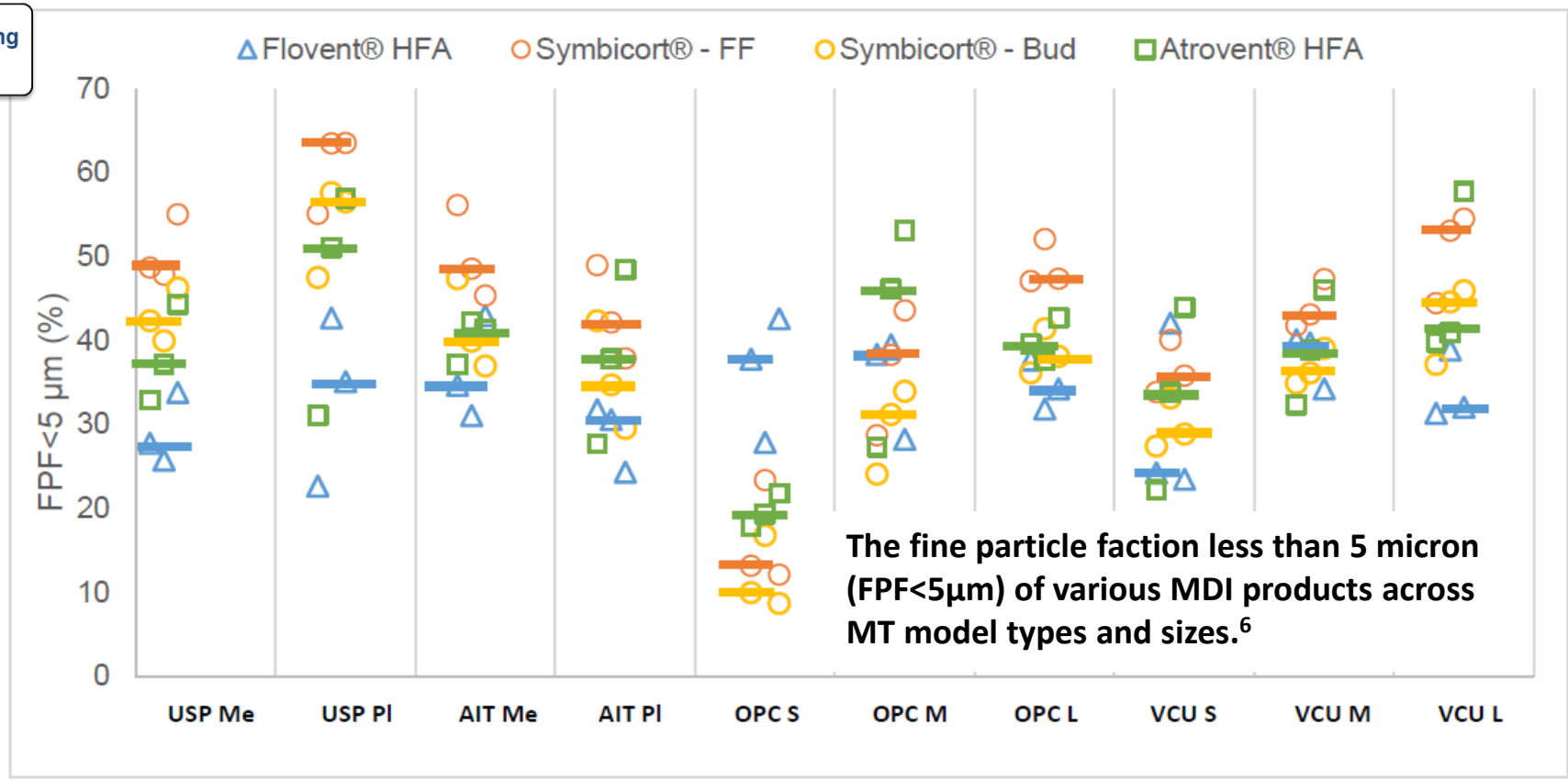
 APSD: aerodynamic particle size distribution; VCU: Virginia Commonwealth University; OPC: Oropharyngeal Consortium

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.[6]

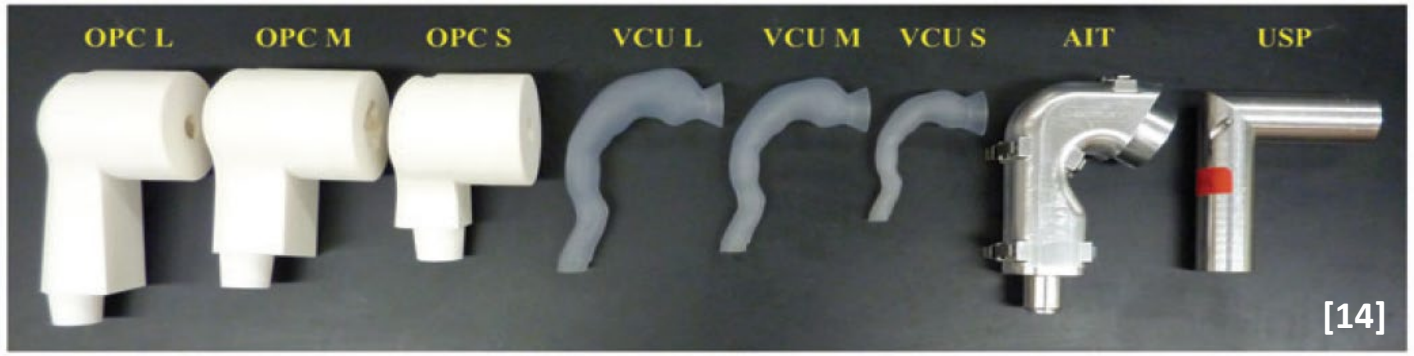


The fine particle faction less than 5 micron (FPF<5µm) of various MDI products across MT model types and sizes.[6]

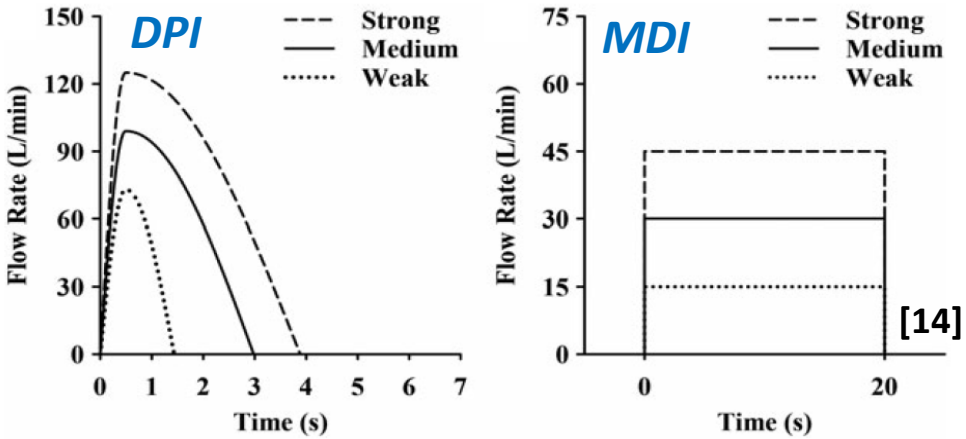
GDUFA: Generic Drug User Fee Amendments; USP: United States Pharmacopeia; AIT: Albert Idealized Throat; OPC: Oropharyngeal Pharmacopeia Consortium; VCU: Virginia Commonwealth University

Realistic APSD Study Design Considerations

Realistic mouth-throat (MT) models



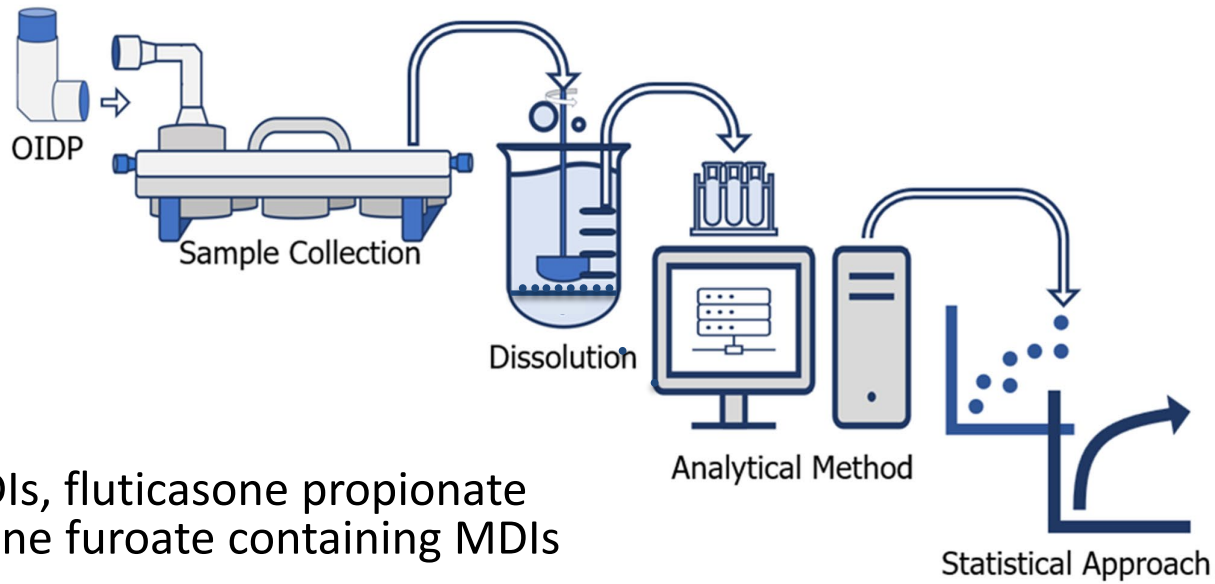
Inhalation profiles (IPs)



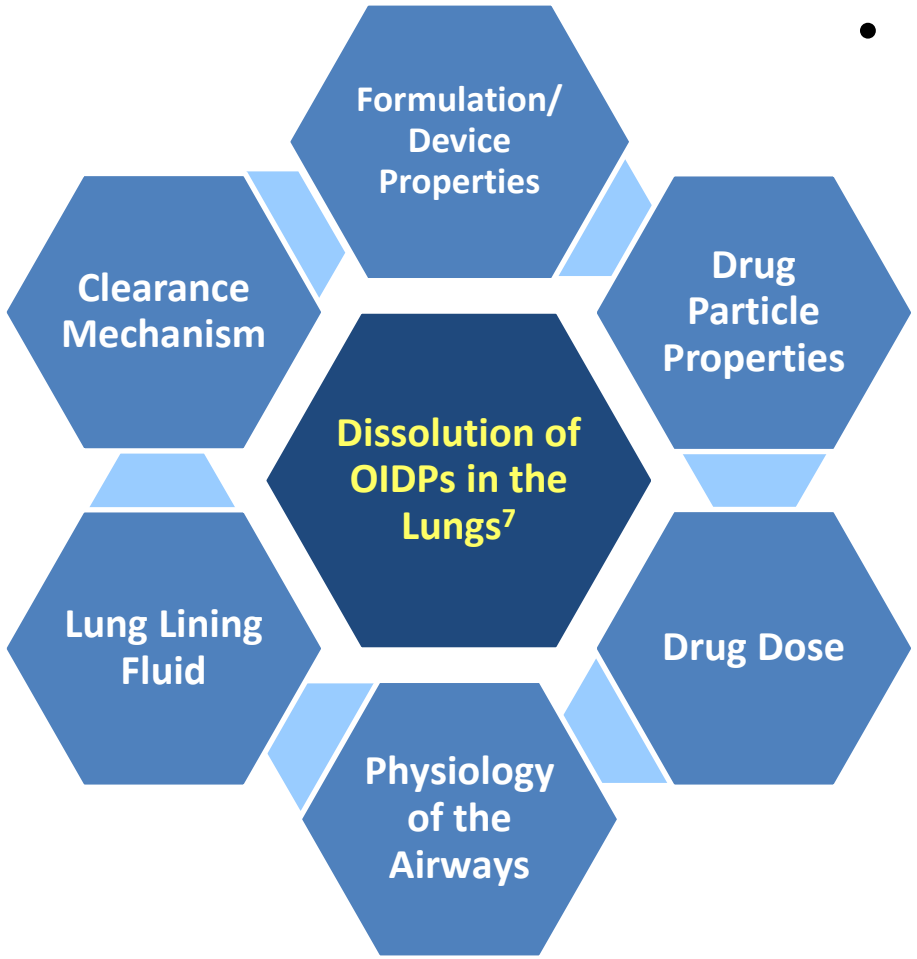
- **PSG Recommendations:**
  - **Beginning** lifestage.
  - Include different ***MT sizes*** and ***IPs*** that reasonably cover the expected inter-subject variability of the indicated patient population via **bracketing approach.**
    - Example: Small and large MT sizes + weak and strong IPs the cover 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-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

- **Dissolution** of the active pharmaceutical ingredient (API) from the emitted dose:
  - Helps to understand the ***rate at which the API dissolves.***
  - Is recommended ***only*** for those cases for which:
    - The ***API is dissolution-limited***, i.e., dissolution is the rate-limiting step in absorption in the lungs, or
    - Contains other ***formulation properties*** that ***make dissolution the rate-limiting step*** in absorption in the lungs.
      - Examples: budesonide containing MDIs, fluticasone propionate containing MDIs and DPIs, mometasone furoate containing MDIs and DPIs.

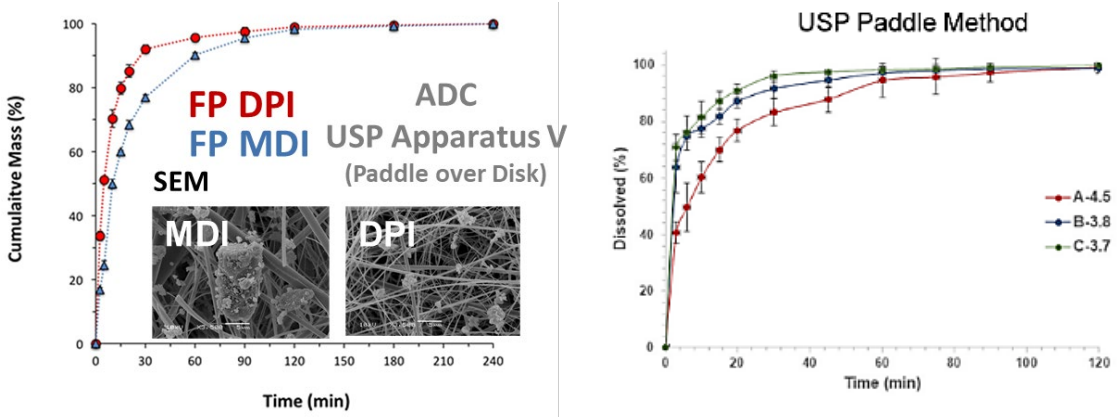


Dissolution Study Design Considerations



Drug dissolution in the lungs can be impacted by multiple factors.[15]

- **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.***



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

Dissolution Study Design Considerations

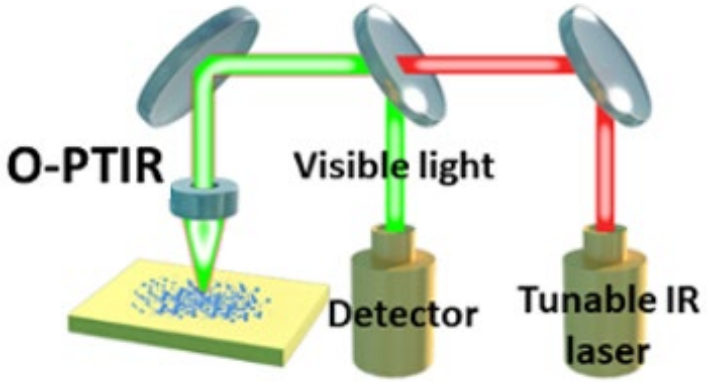
- Sample Collection
- Dissolution Apparatus
- Dissolution Media
- Method Validation
- Assessment

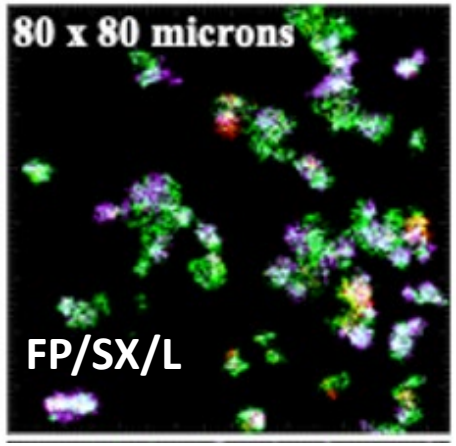
- **PSG Recommendations:**
  - ***Beginning*** Lifestage.
  - Collect **aerosolized dose** of ***similar drug mass*** between T and RS products.
  - **Optimized** and **validated** method (e.g., apparatus, sample collection, dose, media type and volume, stirring/agitation rate, sampling times).
  - **Discriminatory**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

Comparative Characterization Study: Particle Morphology

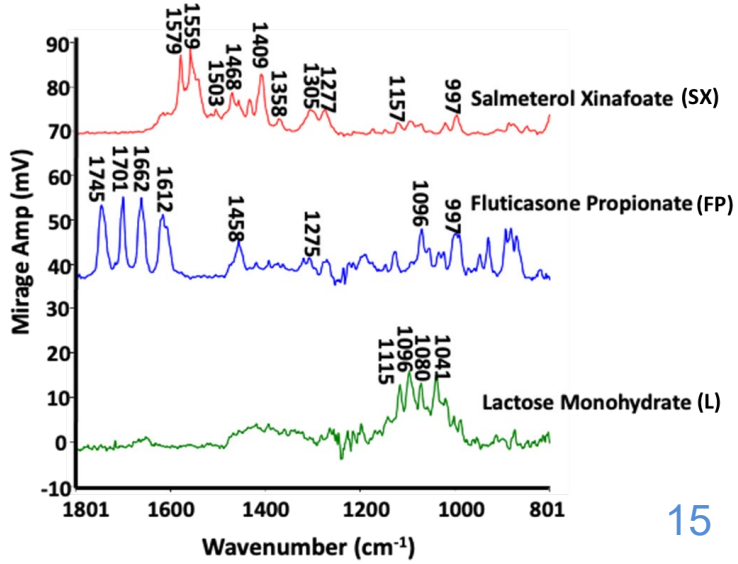
- **Particle Morphology**
  - Particle ***shape***, ***surface roughness***, ***porosity***, ***crystalline/amorphous structure***, etc. of the residual aerosolized dose, once deposited in the lungs, can impact the rate of ***dissolution*** of the API and ***cellular permeability*** and ***uptake*** within the lungs.
  - Compare the residual particle morphology, agglomeration behavior, amorphous/crystalline content, and/or polymorphs and for those cases with ***complex formulation considerations***.

Analysis of Fluticasone Propionate (FP); Salmeterol Xinafoate DPI by Optical Photothermal Infrared Spectroscopy (O-PTIR).[16]





NGI Stage 3



Particle Morphology of the Emitted Dose Study Considerations

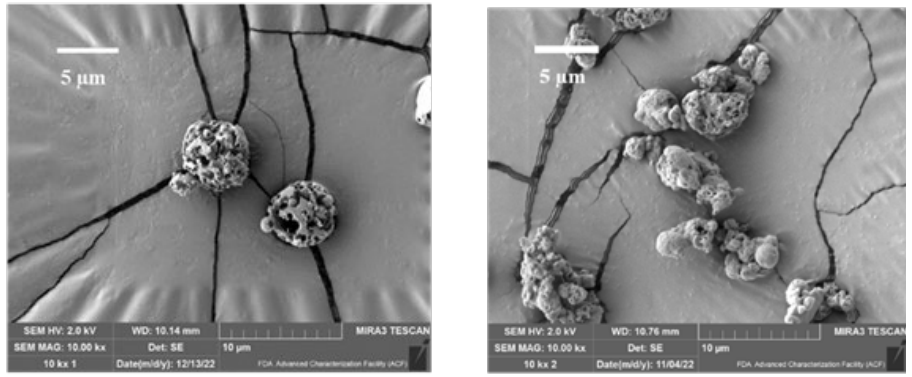
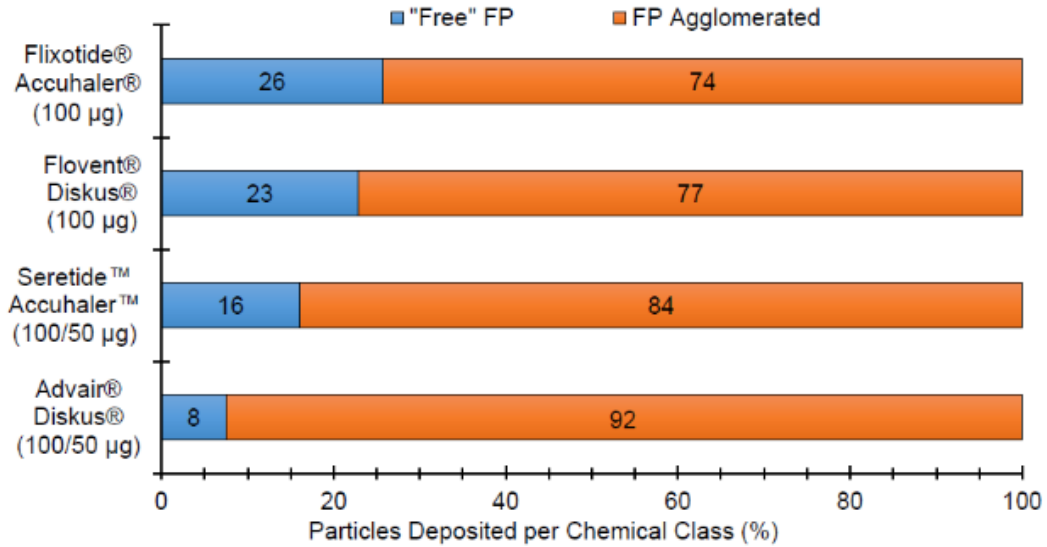
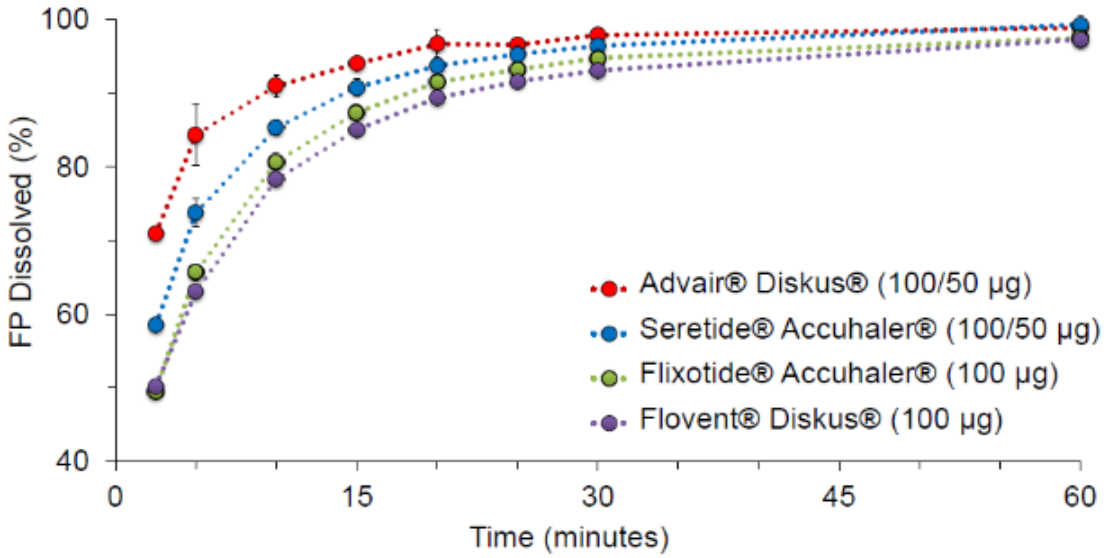


Figure 7: SEM images of phospholipid porous particles found in a marketed DPI (left) and MDI (right) [21]

- ***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.



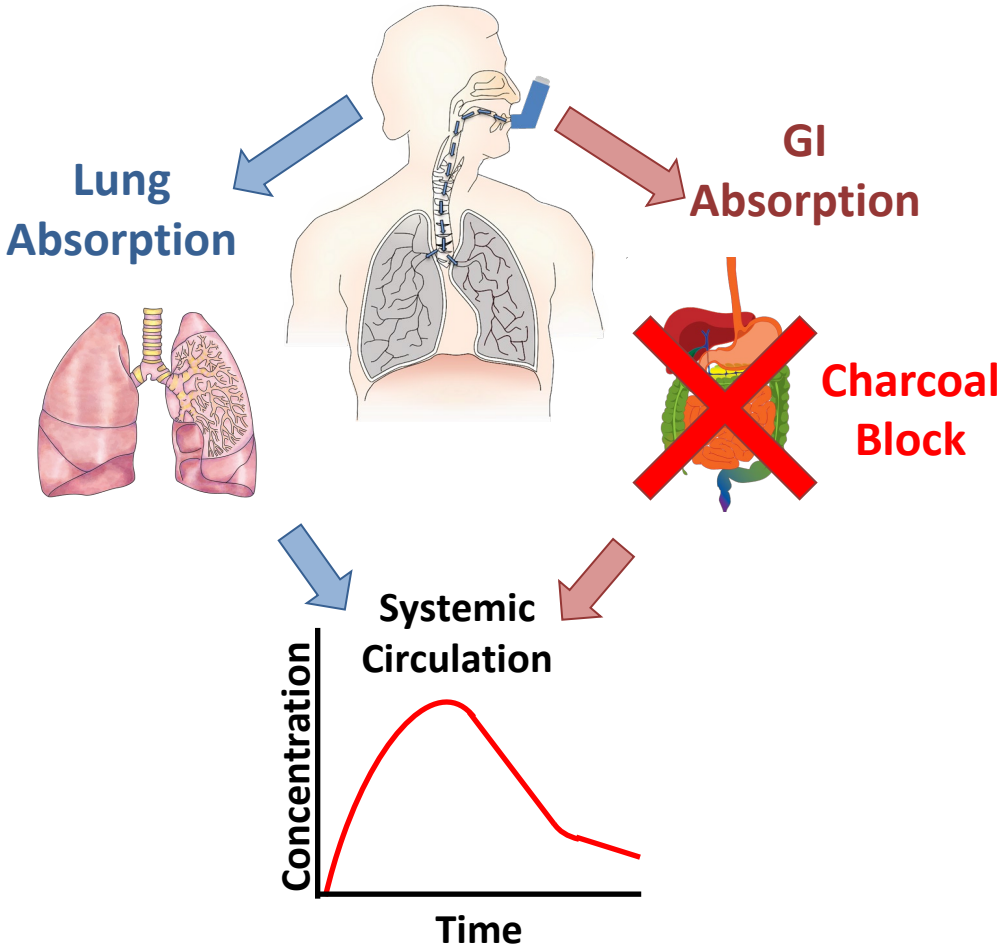


Microstructural differences in the deposited particle agglomerates (left) may be one potential contributing factor to performance differences, such as with dissolution performance (right).[1]

Particle Morphology of the Emitted Dose 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.

In Vivo Charcoal Block PK BE Studies



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.

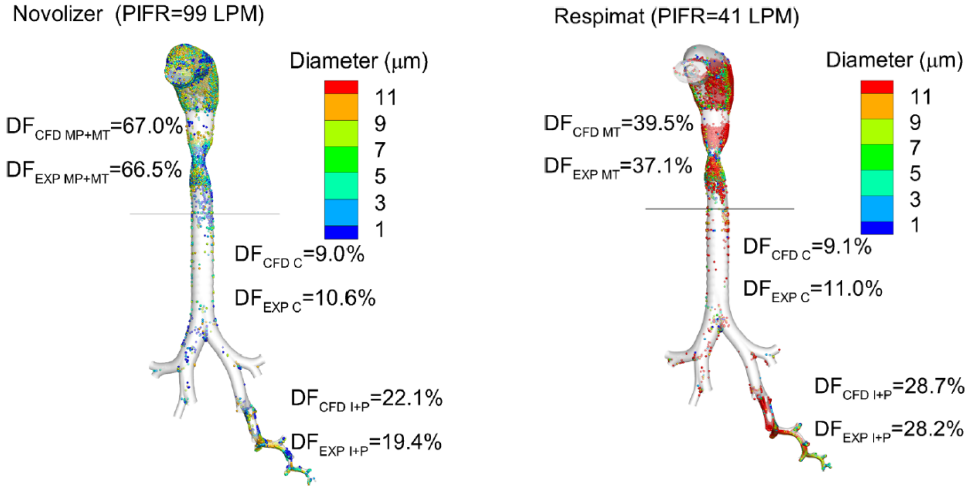
- For OIDPs, a portion of the emitted dose may be swallowed rather than inhaled and end up in the GI tract.
- For drugs with significant gut absorption, systemic levels may be difficult to distinguish between inhaled vs. swallowed portions.
- ***Charcoal block PK studies*** allow for a more direct analysis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

In Vivo Charcoal Block PK BE Study Considerations

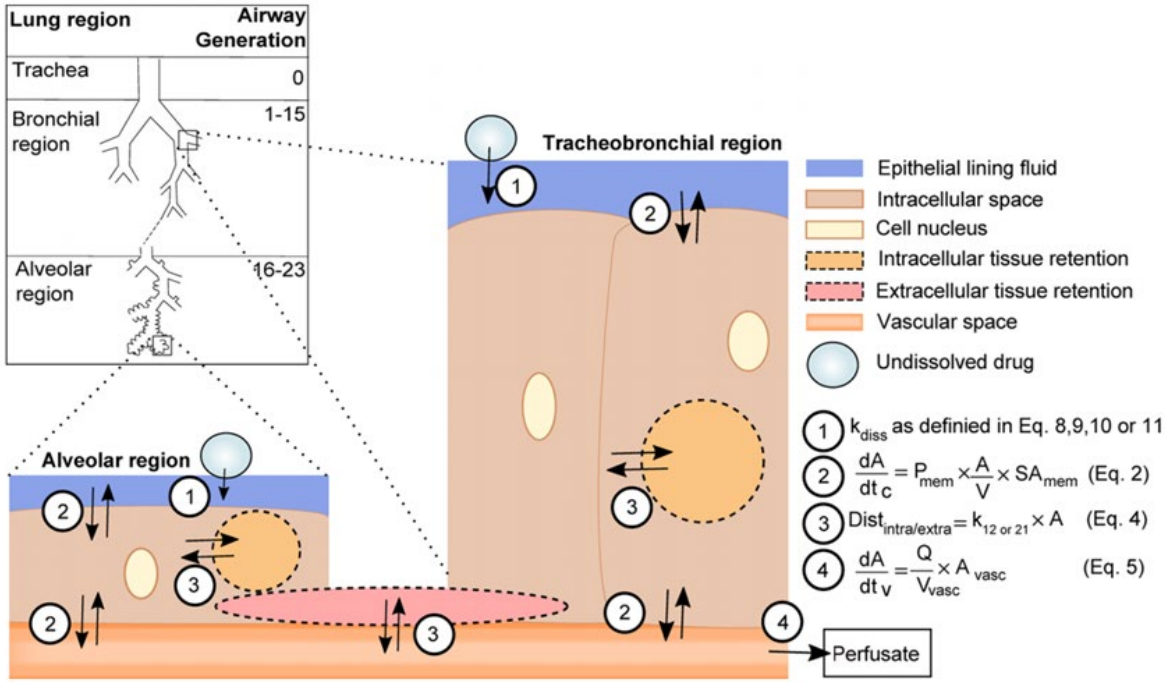
- **PSG Recommendations:**
  - Similar to a PK BE study in many aspects.
    - ***Healthy*** adult male and female subjects.
    - ***Minimum number of inhalations*** to sufficiently characterize the PK profile with a sensitive analytical method.
    - Dose administration should follow the approved labeling 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 abbreviated new drug application (ANDA).
  - **BE:** 90% confidence interval (CI) for the T/R ratios of AUC and C_{max} being between 80 – 125%.
  - Prospective applicants are encouraged to discuss ***other approaches*** for assessing BE in local and systemic bioavailability of the active ingredient with FDA via a pre-ANDA meeting request **before conducting** a charcoal block PK BE study.

Optional Computational Model(s) as Supportive Studies

- ***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**.



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.[17,18]



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).[19]

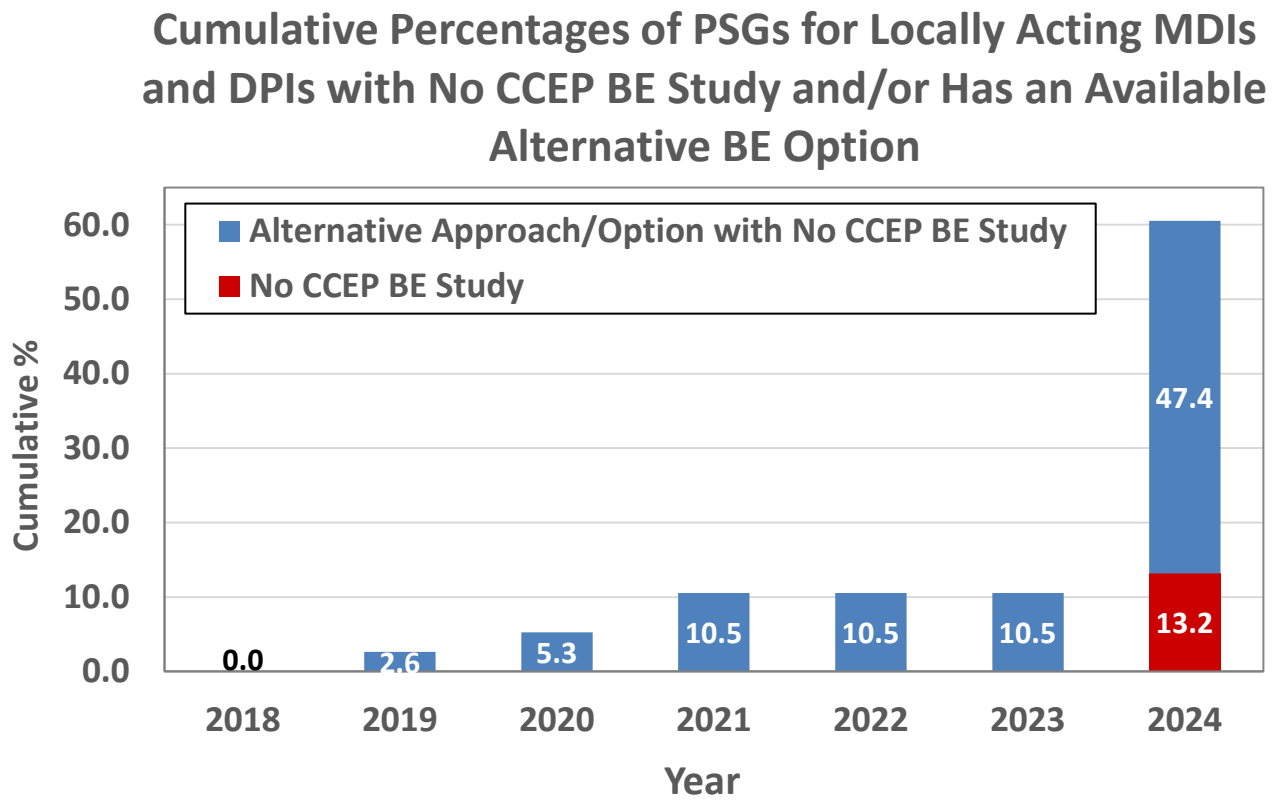
Current Challenges and Future Directions

- **Need for method standardization.**
  - rAPSD: which MT models and IPs to use for bracketing.
  - Dissolution: sample collection, dissolution apparatus, dissolution media, etc.
  - Charcoal PK BE Studies: standardization of charcoal dosing.
- **Establish validated in silico methods to support BE evaluation of OIDPs.**
- **Find areas to streamline and harmonize BE approaches globally for OIDPs.**
  - Identify key vs. supportive BE studies.
  - Establish in vitro-in vivo relationships.
- **Provide additional guidance and clarity where warranted.**

- FDA continues its efforts to address these challenges.
- Refer to most recent PSGs on MDIs and DPIs which are updated periodically and will reflect the Agency's current scientific thinking.
- Prospective applicants are highly encouraged to discuss their development plans with the Agency to gain feedback.

Updates to PSGs of Locally Acting MDIs and DPIs

- Since 2018, FDA has **increased the percentage of available PSGs** for locally acting MDIs and DPIs.
  - Recommend ***alternative approaches*** to CCEP BE studies.
  - An ***option-based*** BE approach (no CCEP/PD BE study in Option 1)
  - ***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:**
  - **13.2%** - PSGs with no recommended CCEP BE study.
  - **47.4%** - alternative approach/option available.
  - Total → **60.5%**



 PSG: product-specific guidance; MDI: metered dose inhaler; DPI: dry powder inhaler; CCEP: comparative clinical endpoint; BE: bioequivalence; PD: pharmacodynamic

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 and workshops to identify ***alternative approaches*** that can be used in lieu of the CCEP BE study for establishing local drug delivery equivalence.
- FDA recently developed ***PSGs for MDIs and DPIs*** that recommend an ***option-based BE approach.***
  - Study recommendations are included for ***rAPSD***, ***dissolution***, ***comparative characterization studies***, ***charcoal block PK BE studies***, and ***computational models.***
- While FDA's option-based BE approaches allow for BE pathways without a CCEP BE study, FDA will continue its efforts to ***clarify***, ***streamline***, and ***harmonize*** its BE approaches for OIDPs.

Acknowledgements

- FDA/CDER/OGD/ORS
  - Bryan Newman
  - Susan Boc
  - Liangfeng Han
  - Anubhav Kaviratna
  - Ross Walenga
  - Steven Chopski
  - Andrew Babiskin
  - Darby Kozak
  - Markham Luke
  - Liang Zhao
  - Lei Zhang
  - Robert Lionberger
  - David McChesney
- 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/OPQ/OPQR
  - Changning Guo
- 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
  - Mark Banaszak Holl
  - Agisilaos Kourmatzis
  - Narender Singh

Questions?

Elizabeth Bielski, MS PhD
Senior Pharmacologist
Division of Therapeutic Performance 1, Office of Research and Standards
Office of Generic Drugs| CDER | U.S. FDA

Elizabeth.Bielski@fda.hhs.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Resources

1. Mangal, S., et al. Microstructural Mapping of Dry Powder Inhalers (DPIs) using Morphologically Directed Raman Spectroscopy (MDRS): A Novel Analytical Tool for DPI Characterization. In: AAPS Annual Meeting, 2018, Washington DC, USA. Poster presentation.
2. Bachhav, S., et al. Systematic Evaluation of the Effect of Formulation Variables on In Vitro Performance of Mometasone Furoate Suspension-Metered Dose Inhalers. *AAPS J.* 2022. 24(9). https://doi.org/10.1208/s12248-021-00638-1.
3. Singh, G., et al. Effect of Inflow Conditioning for Dry Powder Inhalers. *International Journal of Pharmaceutics.* 2021. 608(25). https://doi.org/10.1016/j.ijpharm.2021.121085.
4. Singh, N., et al. Predicting Systemic and Pulmonary Tissue Barrier Concentration of Orally Inhaled Drug Products. *bioRxiv.* 2022. 483633. https://doi.org/10.1101/2022.03.10.483633.
5. Dhapare, S., et al. Factors Influencing Plume Characteristics of Metered Dose Inhalers (MDIs) Following Passage Through Bio-relevant Mouth-Throat Models. *Respiratory Drug Delivery 2021*. 2021, 1: 301-306.
6. Dhapare, S., et al. Effects of Realistic In Vitro Test Factors on the Aerosol Properties of Metered-Dose Inhalers (MDIs). *Drug Delivery to the Lungs.* 2021. 32.

Resources

7. Hochhaus, G. Development of on Optimized Dissolution Test System for OINDPs [Presentation 1], Session 1: Predictive Dissolution Methods for OINDPs, Part 1: https://collaboration.fda.gov/p4x8n2ijonv/ , FDA Workshop: New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products, 2018 Jan 9; FDA White Oak Campus, Link: https://www.fda.gov/drugs/news-events-human-drugs/new-insights-product-development-and-bioequivalence-assessments-generic-orally-inhaled-and-nasal.
8. Price R., et al. Development of an Aerosol Dose Collection Apparatus for In Vitro Dissolution Measurements of Orally Inhaled Drug Products. *AAPS J*. 2020 Mar;22:1-9.
9. Hochhaus, G., et al. Can Pharmacokinetic Studies Assess the Pulmonary Fate of Dry Powder Inhaler Formulations of Fluticasone Propionate? *AAPS J*. 2021 May;23:1-4.
10. RDD Online, *Realistic Mouth Throat Models in Three Sizes*, https://www.rddonline.com/rdd/rdd.php?sid=105.
11. Emmace, *Anatomical Throat Models – OPC Throat Models*, https://www.emmace.se/products/anatomical-throat-models/.
12. 2023 Copley Scientific Limited, *APSD of Metered Dose Inhalers (MDIs),* https://www.copleyscientific.com/inhaler-testing/aerodynamic-particle-size-distribution-apsd/apsd-of-metered-dose-inhalers-mdis/mdis-bais/.

Resources

13. Copley, *Breathing Simulators*, https://www.copleyscientific.com/inhaler-testing/ancillaries/breathing-simulators/brs-300i/.
14. Wei X, Hindle M, Kaviratna A, Huynh BK, Delvadia RR, Sandell D, Byron PR. In Vitro tests for Aerosol Deposition. VI: Realistic Testing with Different Mouth–Throat Models and In Vitro—In Vivo Correlations for a Dry Powder Inhaler, Metered Dose Inhaler, and Soft Mist Inhaler. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*. 2018 Dec 1;31(6):358-71.
15. Amini E, Hochhaus G. Dissolution and Drug Release. In Inhaled Medicines 2021 Jan 1 (pp. 225-266). Academic Press.
16. Khanal D, Tanzina Haque S, Joseph B, Bielski E, Newman B, Yilmaz H, Ahmed S, Boc ST, Chan H, Banaszak Holl M. *Respiratory Drug Delivery 2024*. Volume 1, 2024: 499-503.
17. Tian G, Hindle M, Lee S, Longest PW. Validating CFD Predictions of Pharmaceutical Aerosol Deposition With In Vivo Data. *Pharmaceutical research*. 2015; 32(10): 3170-87.
18. Eriksson J, Thörn H, Sjögren E, Holmstén L, Rubin K, Lennernäs H. Pulmonary Dissolution of Poorly Soluble Compounds Studied in an Ex Vivo Rat Lung Model. *Molecular Pharmaceutics*. 2019; 16(7): 3053-64.
19. Draft Product-Specific Guidance (PSG) on *Formoterol Fumarate; Glycopyrrolate Inhalation Aerosol; Metered* (NDA 208294); Link: https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_208294.pdf.