Product-Specific Considerations for Alternative Bioequivalence (BE) Approaches to Comparative Clinical Endpoint BE Studies

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval
Day 2, Session 2: Nasal and Inhalation Products

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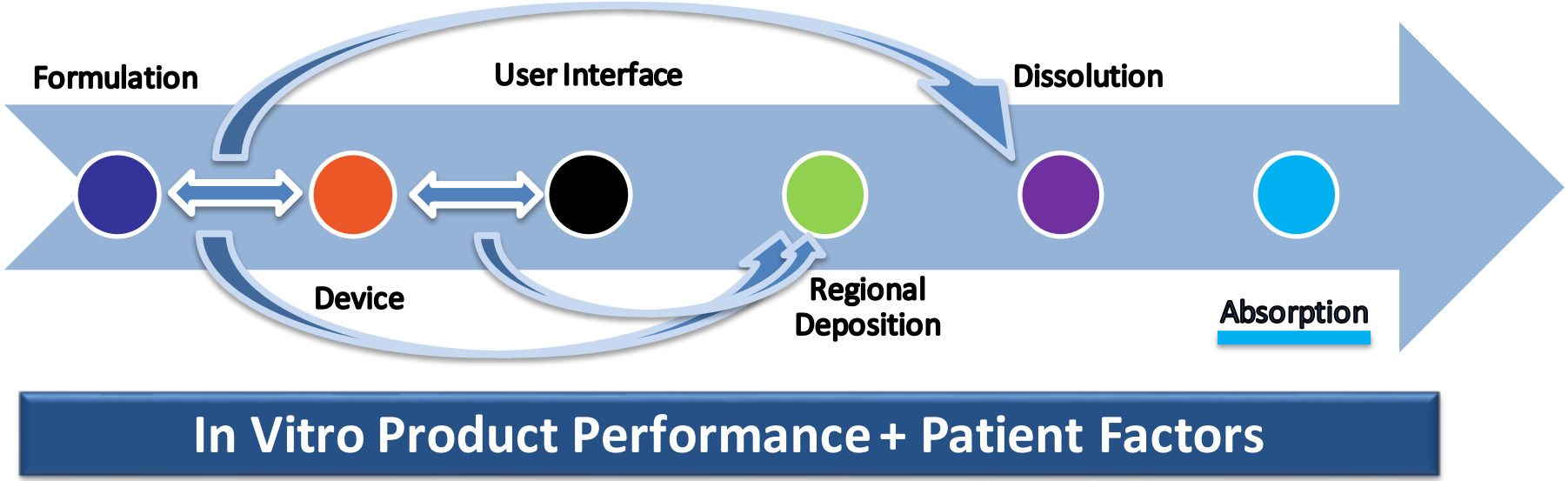
Learning Objectives

- Describe the approach to establish bioequivalence (BE) for orally inhaled and nasal drug products (OINDPs)
- Explain the alternative approaches to the Comparative Clinical Endpoint (CCEP) or Pharmacodynamic (PD) BE studies for orally inhaled drug products (OIDPs)
- Describe the multiple processes contributing to local drug delivery for different dosage forms of OIDPs
- Discuss the importance of product-specific considerations for OIDPs

OINDPs: Orally Inhaled and Nasal Drug Products
OIDPs: Orally Inhaled Drug Products

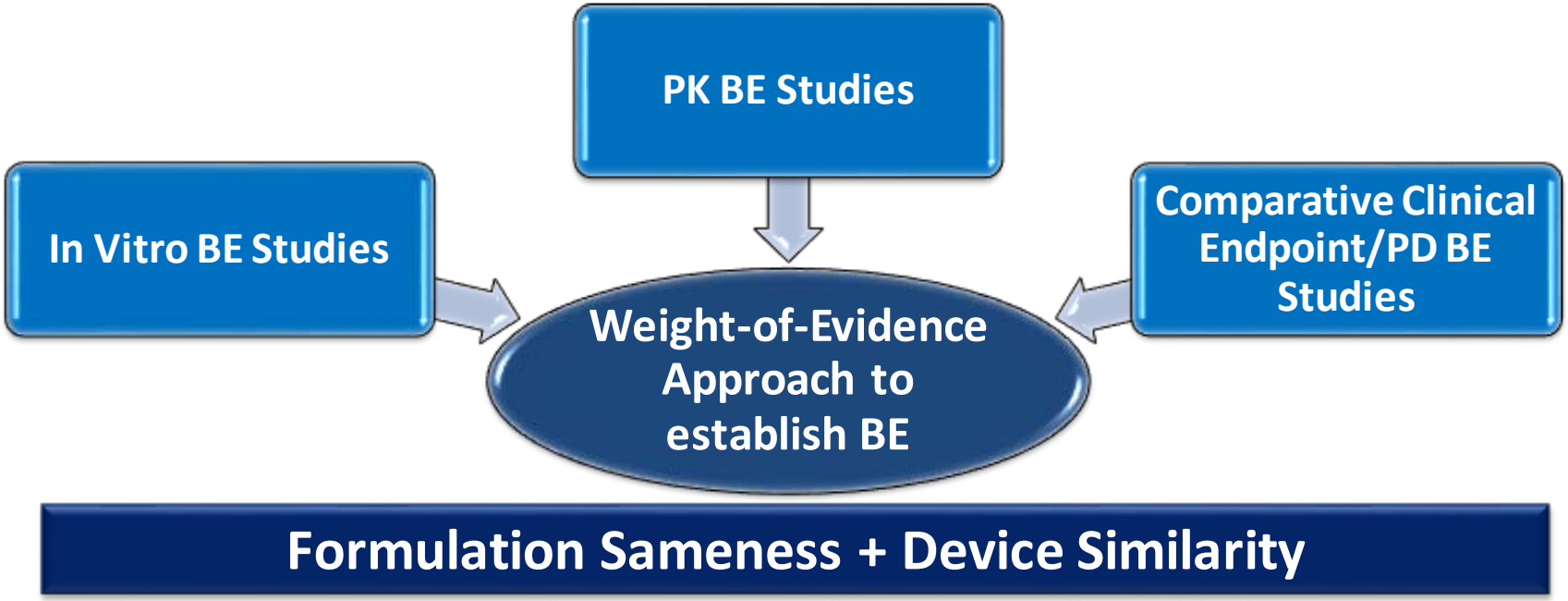
Locally-Acting OINDPs: Challenges for Establishing BE

- Developing generics for **locally-acting OINDPs** is challenging because of the ***multiple factors that can influence drug delivery to the site of action***



Establishment of BE for OINDPs

- **To address challenges for locally-acting OINDPs → *Weight-of-Evidence Approach***
  - ***Locally-acting nasal suspensions, metered dose inhalers (MDIs), dry powder inhalers (DPIs)***



PK: pharmacokinetic
PD: pharmacodynamic

Comparative Clinical Endpoint/PD BE Study for OIDPs

- ***Challenges*** surrounding CCEP or PD BE studies in the weight-of-evidence approach for MDIs and DPIs
  - **Higher variability and lower sensitivity** for evaluation of formulation differences than other BE methods since studies rely on potentially more variable patient population
  - **Longer study duration and more costly** than other types of BE studies
- **FDA's regulations** direct us to the most accurate, sensitive, and reproducible BE methods

Alternative BE Approaches

Considerations for Alternative BE Approaches for OIDPs

- Local delivery of the active pharmaceutical ingredient (API) to the site of action is a complex, multi-step process with each step impacting the next
- The CCEP/PD BE study incorporates ***all steps*** from actuation to deposition when evaluating whether a T or R OIDP have equivalent local drug delivery
- A ***combination*** of in vitro, in silico, and/or alternative in vivo (e.g., PK BE study) studies may account for the different step/factors impacting local delivery of the API to the site of action
  - Proposed studies should **work together** to provide a **comprehensive evaluation of the local drug delivery**, in order to establish equivalence
  - In silico approaches may be useful for demonstrating how results from different alternative BE studies work together to establish equivalence in local drug delivery

The types of alternative BE studies to include may depend on the ***specific OIDP dosage form*** and ***formulation***

Product-Specific Considerations for Alternative BE Approaches for OIDPs

Solution MDIs	***Dissolved*** API in formulation inside canister	Propellant-driven	***Evaporation*** of propellent/co-solvents	Residual API ***particles*** and/or API-cosolvent ***droplets***
Suspension MDIs	***Suspended*** API in formulation inside canister	Propellant-driven	***Evaporation*** of propellent/co-solvents	Residual API ***particles***
DPIs	Blended ***powder*** API formulation in capsule/blister/ reservoir	With ***patient inhalation***	***Deaggregation*** from carrier particles	Residual API and API-carrier agglomerate ***particles***

Alternative BE Approach: Solution MDIs

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

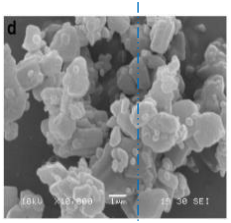
Actuation, Aerosol formation	**Characterization of Emitted Sprays** (velocity profiles and evaporation rates) • Understand droplet size and evaporation process of formulation emitted from device impact of patient variability
Formulation Post-actuation	**Morphology Imaging Comparisons** (characterization of full range of residual drug particle sizes) • Understand residual particle morphology and size distribution of formulation emitted from the device
Transit through the airways	**More Predictive APSD Testing** (representative mouth-throat models and breathing profiles) • Understand impact of patient variability
Deposition, Dissolution, Absorption	**Dissolution** • Understanding how API dissolved at site of action for absorption once deposited
Methods for further support	**Quantitative Methods and Modeling** (e.g., physiologically-based PK, computational fluid dynamic 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

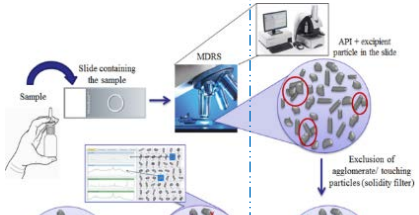
APSD: Aerodynamic Particle Size Distribution

• Product-Specific Guidance (PSG) on *Beclomethasone Dipropionate Metered Inhalation Aerosol* (May 2019) • PSG on *Beclomethasone Dipropionate Metered Inhalation Aerosol* (Mar 2020) • PSG on *Ipratropium Bromide Metered Inhalation Aerosol* (Mar 2021) • PSG on *Ciclesonide Metered Inhalation Aerosol* (Mar 2021)

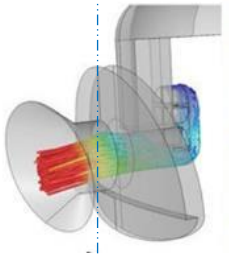
ORS Research Activities for OIDPs

Formulation | **User Interface** | **Dissolution**

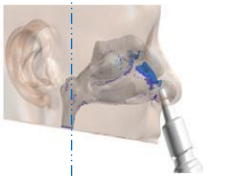


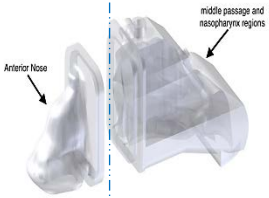


Device



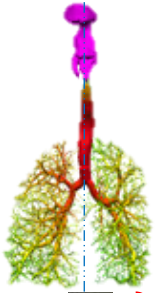
HF CONSIDERATIONS

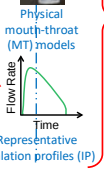


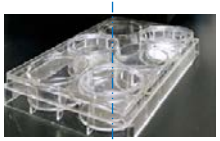


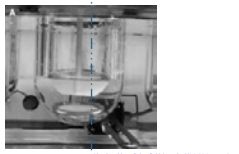
OUTCOME

Regional Deposition

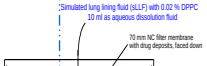


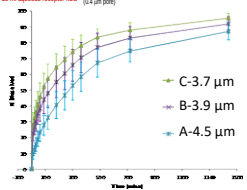




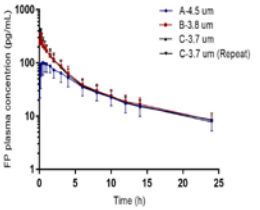


In vitro APSD test more predictive of in vivo deposition





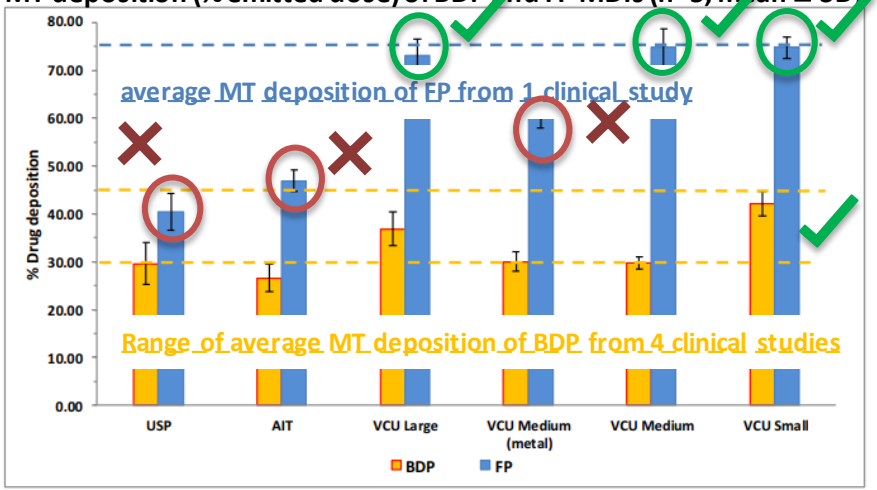
Absorption



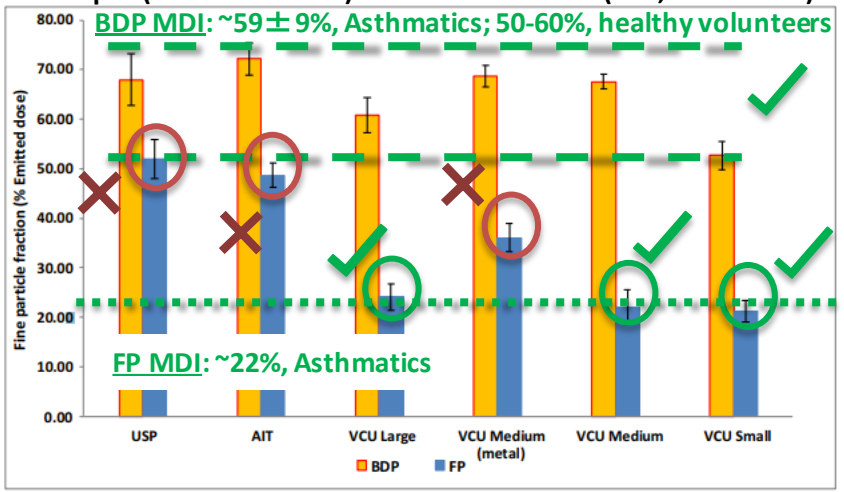
In Vitro Characterization:
Solution vs. Suspension MDIs

- Suspension FP MDIs much more sensitive to variations in MT model vs. solution BDP MDIs
- "In vitro characterization of MDI products could be influenced by many factors, such as the type of *formulation*, the *geometry*, *shape*, *internal space volume*, and the *material* used to make the MT models."
- "bio-relevant MT models can provide important insight about in *vivo performance of MDI products* and could be useful tools to assist…*BE assessments of generic MDI products*"

MT deposition (% emitted dose) of BDP and FP MDIs (n=5, mean ± SD)



FPF<5µm (% emitted dose) of BDP and FP MDIs (n=5, mean ± SD)



AIT: Alberta Idealized Throat; VCU: Virginia Commonwealth University
BDP: Beclomethasone Dipropionate; FP: Fluticasone Propionate

FPF<5µm: Fine particle fraction less than 5 µm

Kaviratna A, et al. *AAPS PharmSciTech* **20**: 130 (2019).

In Vitro Characterization:
Same API, Different DPI Product

MDRS of ISM dose collected with UniDose system via USP inlet port at fixed flow of 60 L/min, 4 s

In vitro dissolution modified USP Apparatus V of ISM dose collected from equivalent 500 mcg FP

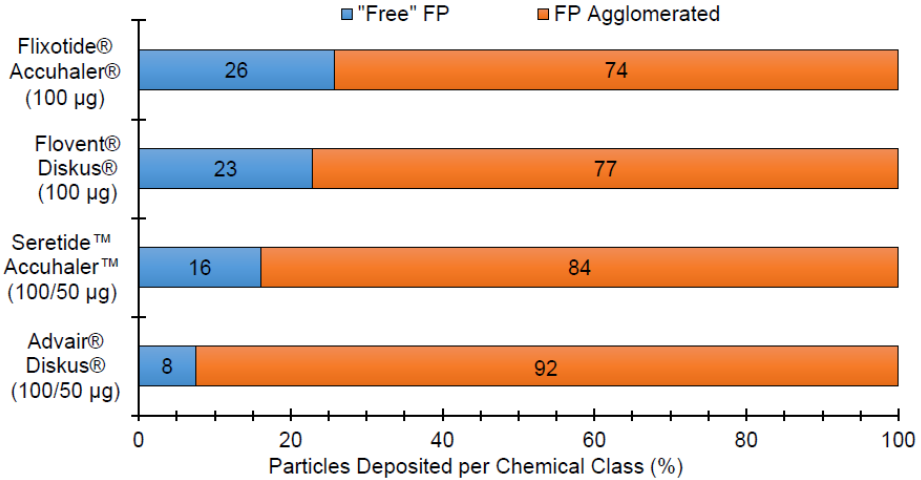


Figure 3: Particles deposited per chemical class (%) of the ISM of Advair® Diskus® (FP/SX; 100/50 µg), Flixotide® Accuhaler® (FP; 100 µg), Flovent® Diskus® (FP; 100 µg), and Seretide® Accuhaler® (FP/SX; 100/50 µg). These are presented as mean ± standard deviation (n=5).

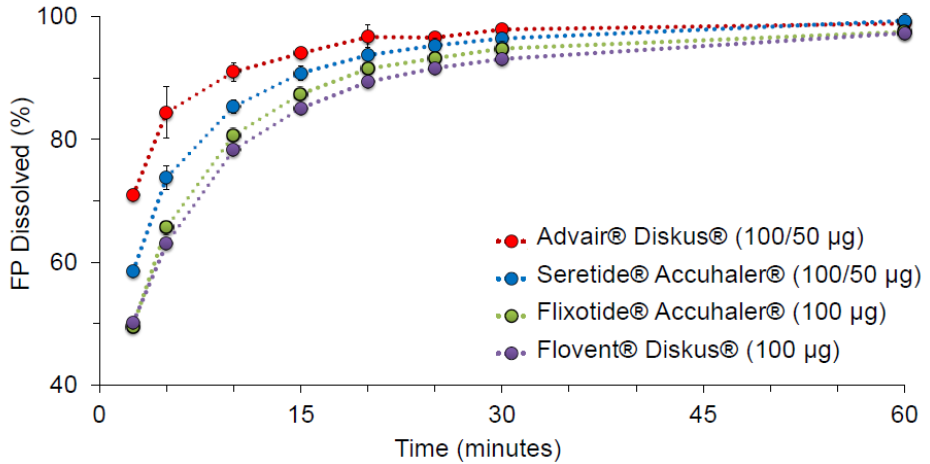


Figure 4: FP dissolved (%) from the ISM of Advair® Diskus® (100/50 µg), Flixotide® Accuhaler® (100 µg), Flovent® Diskus® (100 µg), and Seretide® Accuhaler® (100/50 µg). These are presented as mean ± standard deviation (n=2).

Investigations into formulation microstructure may provide useful information to understand differences between test and reference products.

Mangal S, et al. *AAPS Annual Meeting 2018*. Poster presentation.

ISM: Impactor-sized mass

Alternative BE Approach: Suspension MDIs

The effects of ***suspended API*** particles on the drug delivery process should be considered

- Surface level interactions could impact downstream processes critical for ***regional drug delivery***:
  - Van der Waals or electrostatic forces can lead to **changes in API PSD** over time through agglomeration
  - Surface roughness of the API particles may **impact stability** of the suspension
  - Interaction of API with excipients used for formulation stability may lead to **differences in PSD of dry particles**

Characterization of formulation pre-actuation

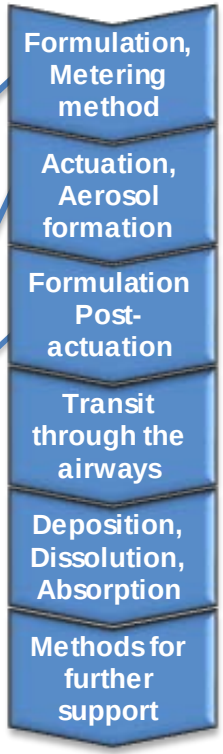
Hypothetical Example

Formulation, Metering method	• **Characterization of the effects of suspended API particles on the drug delivery process**
Actuation, Aerosol formation	• Characterization of Emitted Sprays
Formulation Post-actuation	• Morphology Imaging Comparisons
Transit through the airways	• More Predictive APSD Testing
Deposition, Dissolution, Absorption	• Dissolution
Methods for further support	• Quantitative Methods and Modeling • Alternative PK BE Studies

Alternative BE Approach: DPIs

The effects of the blended **API/carrier** particles and particle **deaggregation** on the drug delivery process should be considered

- May influence regional deposition and rate and extent of drug absorption
- API particles are typically **agglomerated** with themselves or with carrier and other excipient particles
  - Agglomerate profile depends on the physicochemical components in the formulation (e.g., PSD, morphology, surface roughness, cohesive/adhesive forces)
  - May be influenced by manufacturing process
- **Deaggregation** of API from carrier particles with energy generated during patient inhalation
  - Each DPI uses different internal geometries or other mechanisms for aerosolization, resulting in **different resistances to airflow**
  - Patient inspiratory flow provides a **variable energy source** which may be influenced by disease state



Hypothetical Example

- **Characterization of agglomerated API particles prior to actuation**
- Characterization of Emitted Aerosol
  - **Consider different inhalation flow rates**
- Morphology Imaging Comparisons
  - **Comparison of formulated and aerosolized forms**
- More Predictive APSD Testing
- Dissolution
- Quantitative Methods and Modeling
- Alternative PK BE Studies

Newman B, et al. *Pharm Med* **34**, 2:93-102 (2020).

General Considerations for Alternative BE Approaches for OIDPs

- Approaches should address sameness of delivery at the ***site of action***
- Alternative approaches may be proposed
  - If scientific proposal is for a product that does not have a PSG, is outside what is recommended in a PSG, or contains complex development issues, it is ***highly encouraged*** that firms submit a **pre-ANDA Product Development Meeting**
    - Refer to FDA guidance for *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (November 2020)
    - Approaches should be scientifically justified with a comprehensive, significant body of data, and evaluated as statistically meaningfully as possible

Due to the complexity of many different factors that can affect generic product performance, critical key attributes for any MDI or DPI may be ***product-specific*****.** It is vital to understand key quality attributes of your generic product (in vitro performance) in comparison to the RLD that will influence in vivo BE (deposition and absorption of the API to the site of action) as to establish an appropriate alternative BE approach to the CCEP or PD BE study.

Conclusions

- OINDPs are complex drug-device combination products with multiple factors contributing to their performance
- Establishment of BE for **locally-acting OINDPs** occurs through the ***weight-of-evidence approach***
  - CCEP or PD BE, PK and in vitro BE all provide indirect evidence of equivalent local delivery
- The types of studies included as part of an alternative BE approach to a CCEP or PD BE study will be ***product-specific***, as differences in dosage form and formulation will give rise to different areas of uncertainty.
- **Firms are *highly encouraged* to submit a pre-ANDA Product Development Meeting Request for communication and seeking the Agency's feedback and comments on alternative BE study proposals**
  - Approaches should be scientifically justified with a comprehensive, significant body of data, and evaluated as statistically meaningfully as possible

Challenge Question #1

Which of the following statements is NOT true?

A. Comparative clinical endpoint or PD BE, PK and in vitro BE studies all provide indirect evidence of equivalent local delivery.

B. In silico approaches may be useful for demonstrating how results from different alternative BE studies work together to establish equivalence in local drug delivery.

C. The different steps from actuation to deposition do not impact local delivery of the API to the site of action.

D. The types of alternative BE studies to include may depend on the specific OIDP dosage form and formulation.

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Questions?

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Resources

- FDA product-specific guidance on *Beclomethasone Dipropionate Inhalation Aerosol, Metered* [RLD: QVAR RediHaler® (Posted May 2019)].
- FDA product-specific guidance on *Beclomethasone Dipropionate Inhalation Aerosol, Metered* [RLD: QVAR® (Posted Jan 2016; Revised Mar 2020)].
- FDA product-specific guidance on *Ipratropium Bromide Inhalation Aerosol, Metered* [RLD: ATROVENT HFA (Posted Mar 2015; Revised Mar 2021)].
- FDA product-specific guidance on *Ciclesonide Inhalation Aerosol, Metered* [RLD: ALVESCO (Posted Jan 2016; Revised Mar 2021)].
- Kaviratna A, Tian G, Liu X, et al. "Evaluation of Bio-relevant Mouth-Throat Models for Characterization of Metered Dose Inhalers." *AAPS PharmSciTech* 20: 130 (2019).
- Price R, Shur J, Ganley W, et al. Development of an Aerosol Dose Collection Apparatus for In Vitro Dissolution Measurements of Orally Inhaled Drug Products. *AAPS J* 22: 47 (2020).
- Mangal S, Conti DS, Delvadia R, 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.
- Newman B, Witzmann K. Addressing the Regulatory and Scientific Challenges with Generic Orally Inhaled Drug Products. *Pharm Med* 34, 2: 93-102 (2020).
- FDA guidance for industry: Formal Meetings Between FDA and ANDA Applicants of Complex Products under GDUFA (Nov 2020).