Advancements in In Vitro Studies for Alternative Bioequivalence (BE) Approaches to Comparative Clinical Endpoint BE Studies

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 3: Future Directions, Emerging Technology, and Current Thinking on Alternative BE Approaches

Topic 1: Nasal and Inhalation Products

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September 30, 2020

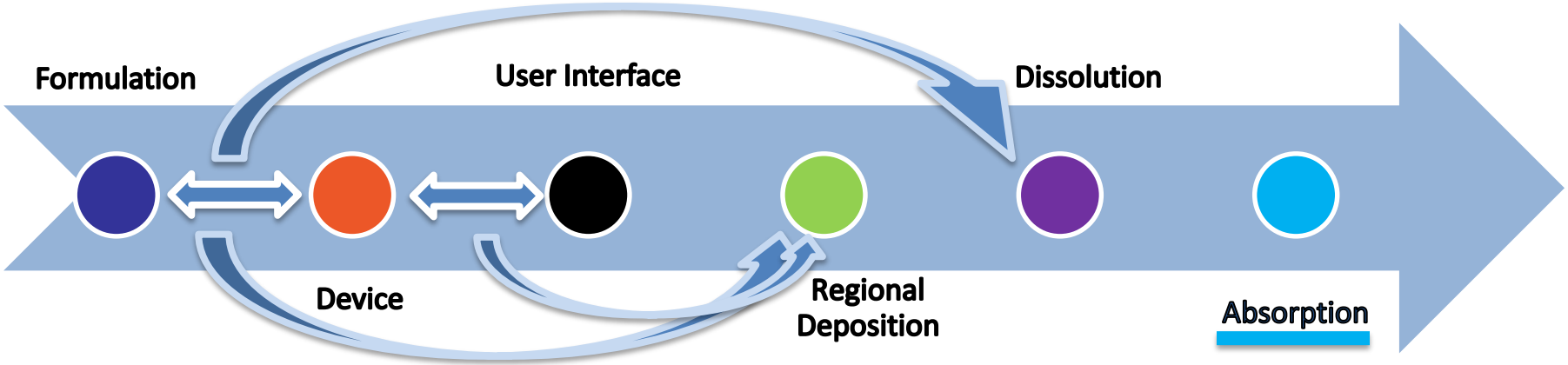
Learning Objectives

- Describe the approach to establish bioequivalence (BE) for OINDPs
- Understand and describe the alternative approaches to the Comparative Clinical Endpoint (CCEP) or Pharmacodynamic (PD) BE studies for OIDPs
- Understand and describe the role and importance of realistic APSD testing for OIDPs
- Understand and describe the role and importance of in vitro dissolution testing for OIDPs

OINDPs: Orally Inhaled and Nasal Drug products;
OIDPs: Orally inhaled drug products;
APSD: Aerodynamic Particle Size Distribution

Locally-Acting OINDPs: Challenges for Establishing BE

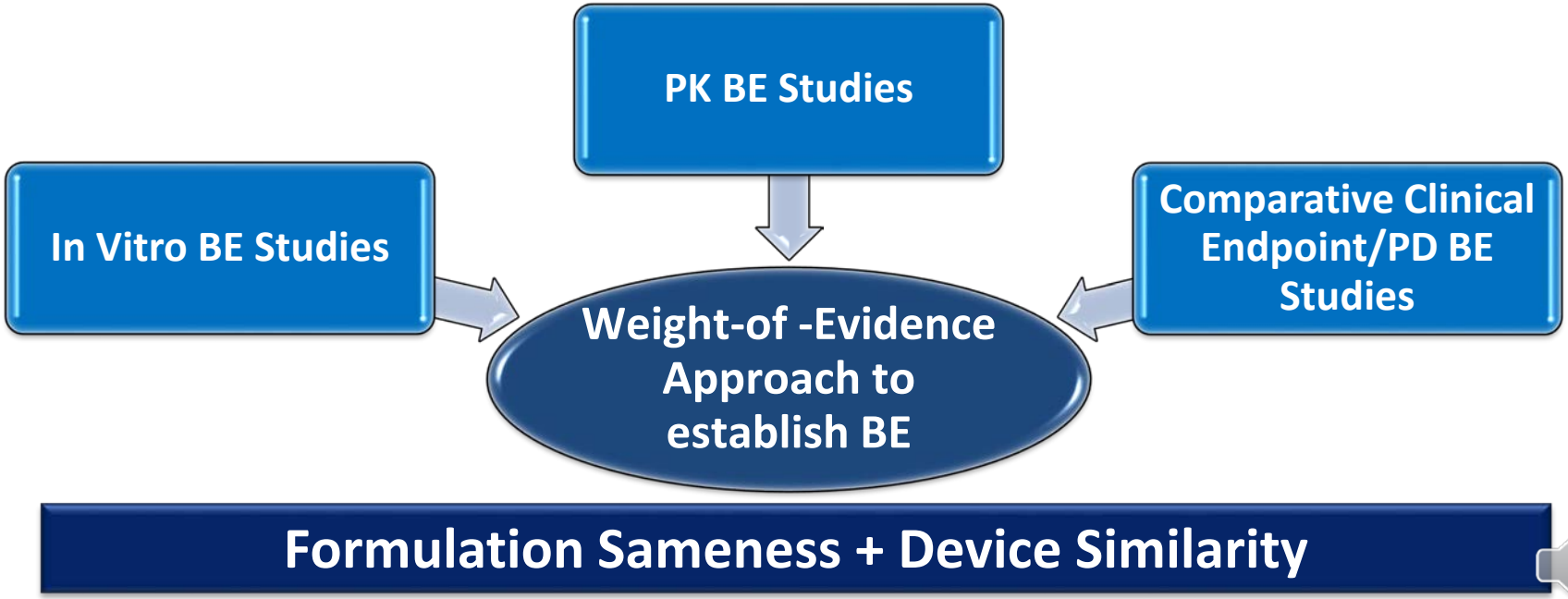
- Developing generics for **locally-acting OINDPs** is challenging because of the ***multiple factors that can influence drug delivery to the site of action***



In Vitro Product Performance + Patient Factors

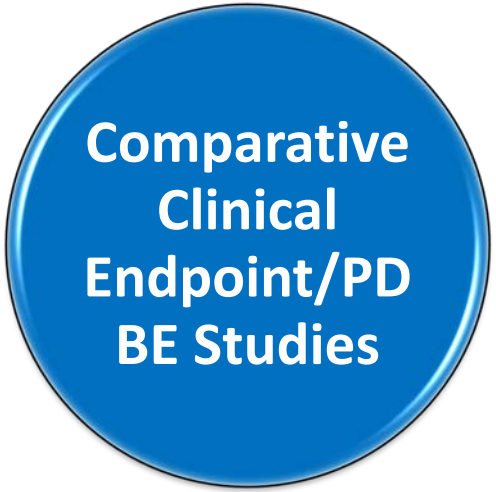
Traditional Approach to Establishment of BE for OINDPs

- **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

Future Role of Comparative Clinical Study for MDIs/DPIs



- Challenges surrounding CCEP or PD BE studies in the weight-of-evidence approach for MDIs and DPIs
  - **Higher variability** of these studies can lead to **lower accuracy and reproducibility** for BE establishment → ***Alternative approaches***
  - **Flat exposure-response** in these studies can lead to **lower sensitivity** for BE establishment → ***Alternative approaches***
  - **FDA's regulations** direct us to the most accurate, sensitive, and reproducible BE methods → ***Alternative approaches***
- Potential alternatives to the CCEP or PD study need to address:
  - The relationship of systemic PK data to local levels of drug within the lungs (site of action)
  - ***The correlation between in vitro performance and in vivo drug deposition (IVIVCs)***
    - Relationship between in vitro performance (dependent on **formulation, device, formulation-device interactions**) to local lung deposition and clinical performance (dependent on **patient factors**)

Alternative Approach: Solution MDIs

Alternative Approaches to CCEP BE study: PSGs for *Beclomethasone Dipropionate Inhalation Aerosol, Metered* [RLD: QVAR Redihaler® (Posted May 2019); RLD: QVAR® (Posted Jan 2016; Revised Mar 2020)

- If a generic shows formulation sameness (Q1/Q2) and device similarity to the RLD, additional supportive information may provide a foundation to help ensure the ***equivalence to local site of action*** (lungs):

More Predictive APSD Testing (representative mouth-throat models and breathing profiles)
- Understand impact of patient variability

Characterization of Emitted Sprays (velocity profiles and evaporation rates)
- Understand droplet size and evaporation process of formulation emitted from the device

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

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

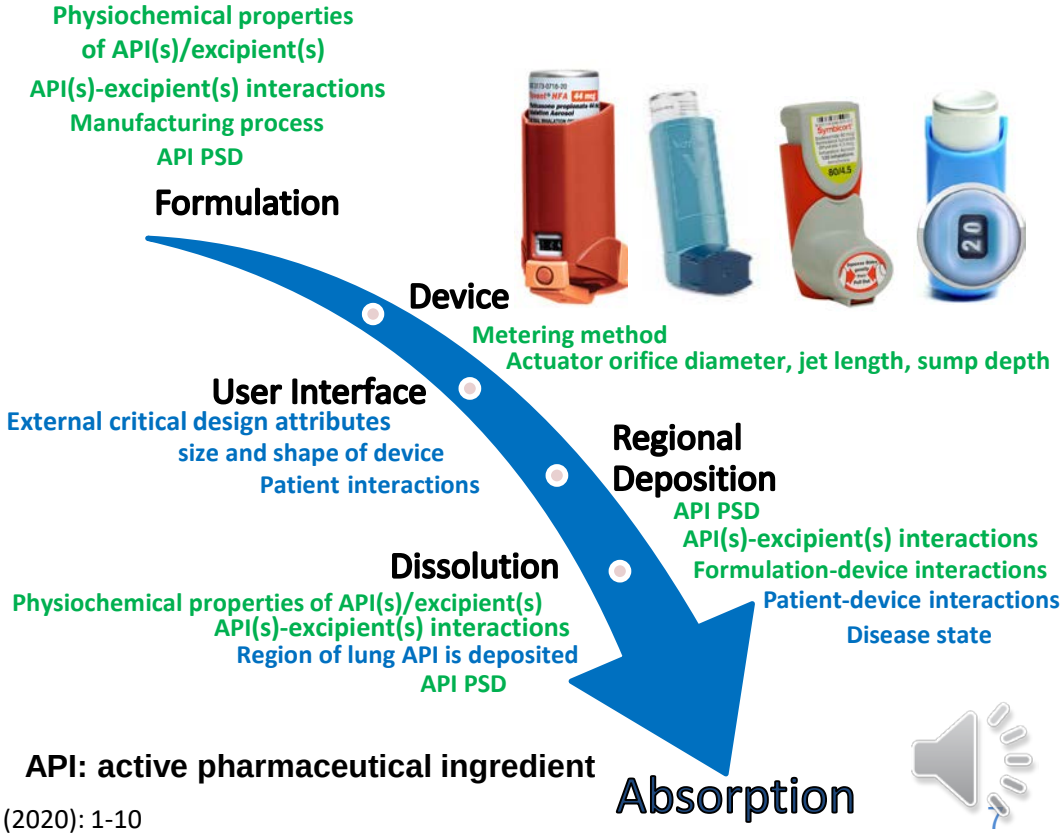
Quantitative Methods and Modeling (e.g., **physiologically-based PK; computational fluid dynamic studies) studies)**

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

RLD: reference listed drug; PSGs: product-specific guidances

Alternative Approach: Suspension MDIs

- **Specific Additional Challenges for Suspension MDIs**
  - Understanding interaction of ***suspended API*** in the canister and emitted from the actuator
    - Formulation, device, formulation-device interactions that influence regional deposition and absorption of the API
      - Manufacturing process
      - Physiochemical properties of API(s)/excipient(s)
      - API particle size distribution (PSD)
      - Excipient(s) (type and amount)
      - Actuator design



Newman, Bryan, et al.. ***Pharmaceutical Medicine*** (2020): 1-10

Alternative 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 issued in a PSG, or contains complex development issues, it is ***highly encouraged*** to the firm to submit a **pre-ANDA Product Development Meeting**
    - Refer to FDA guidance for *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2017)
    - Approaches should be scientifically justified with a comprehensive, significant body of data, and evaluated as statistically meaningful 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 your generic product in comparison to the RLD that will influence in vivo BE as to establish an appropriate alternative BE approach to the CCEP or PD BE study.

ORS Research Activities for OIDPs

Formulation

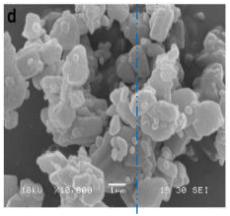
User Interface

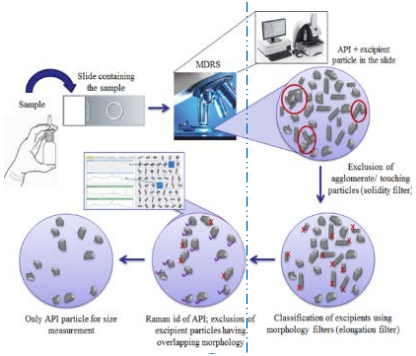
Dissolution

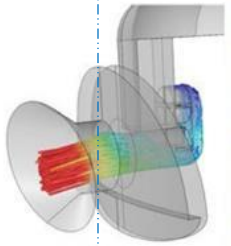
Device

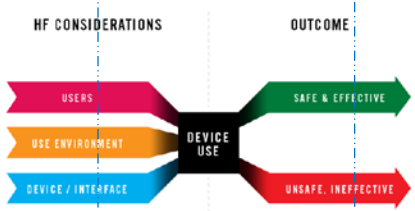
Regional Deposition

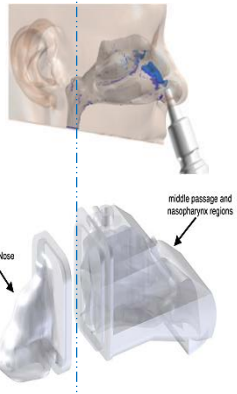
Absorption

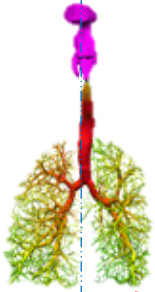


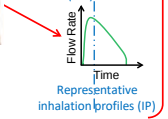


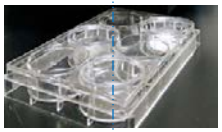


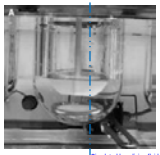




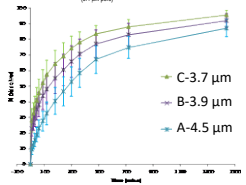


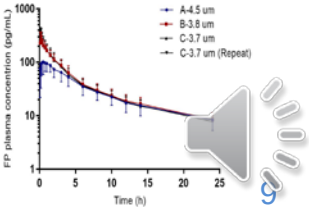






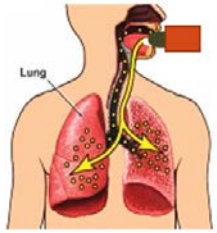
In vitro APSD test more predictive of in vivo deposition





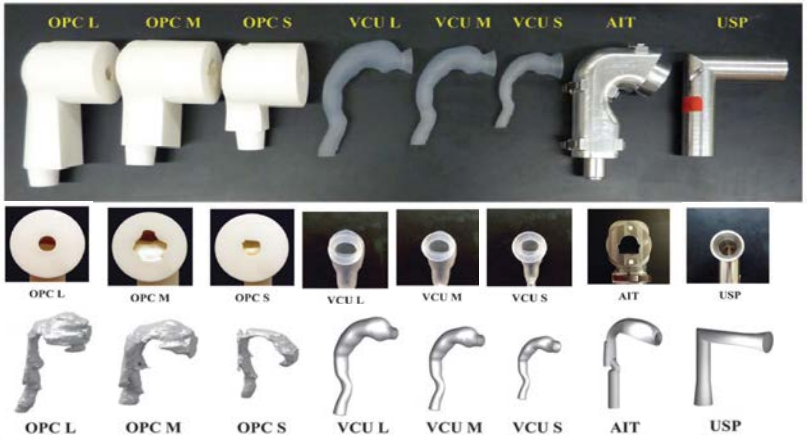
Realistic APSD Testing: Overview

- **A more realistic in vitro APSD method is important as part of alternative BE approach as to understand the *impact of patient variability.***

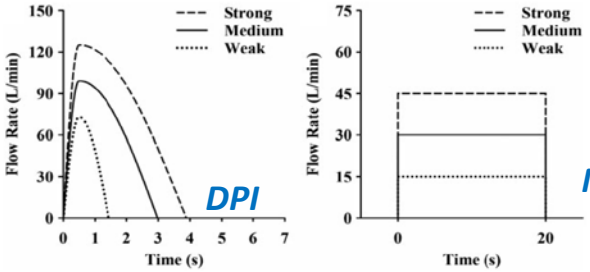


http://images.lifescript.com/images/ebsco/images/inhaled_poison.jpg

Realistic mouth-throat (MT) models



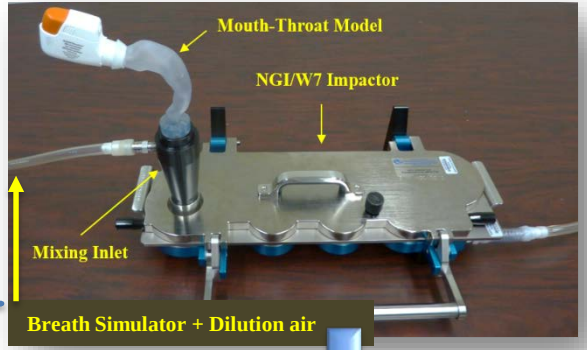
Inhalation profiles (IPs)



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

www.fda.gov

NGI: next generation impactor

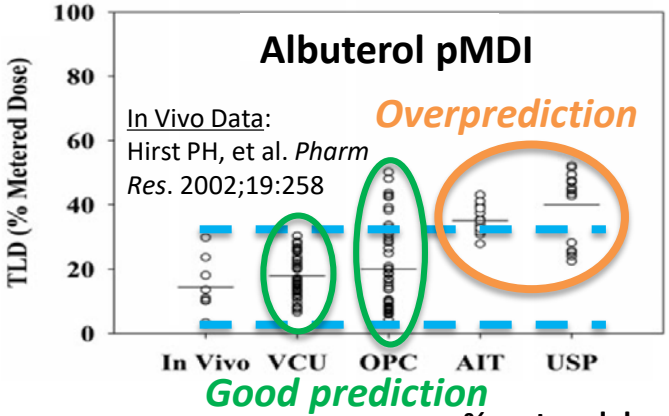


In vitro APSD method more predictive of in vivo deposition

Wei, Xiangyin, et al. *Journal of aerosol medicine and pulmonary drug delivery* 31.6 (2018): 358-371.
https://collaboration.fda.gov/p1qe3izohvy/

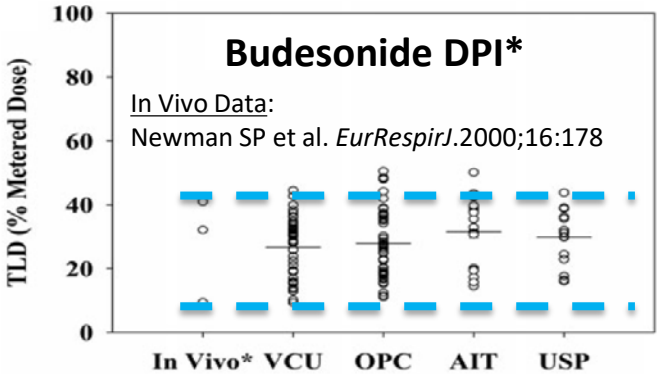
Realistic APSD Testing: In Vitro-In Vivo Comparisons

- **Albuterol (100 µg as sulfate) pMDI; 15-45 L/min**
  - ***Variance of $TLD_{in\ vitro}$ mostly due to MT model***
    - MT selection essential (test across S and L MT models)



% metered dose that escapes MT

- **Budesonide (200 µg) DPI; weak-strong realistic IPs**
  - ***Variance in $TLD_{in\ vitro}$ mostly due to flow conditions (IPs); MT model less important***



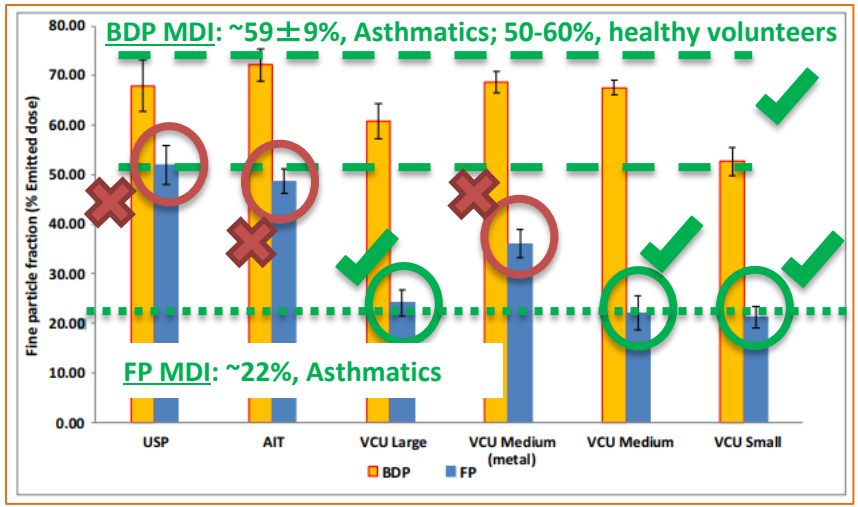
In Vivo* = median and range

Product-specific results: To capture patient variability – include various MT models and IPs

Realistic APSD Testing: Solution vs. Suspension MDIs

BDP: Beclomethasone Dipropionate; FP: Fluticasone Propionate

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



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

- **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*"**

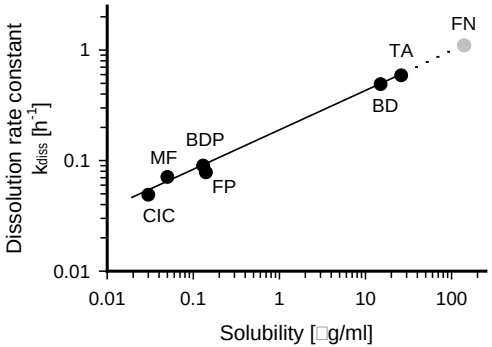
Kaviratna, Anubhav, et al. *AAPS PharmSciTech* 20.3 (2019): 130.

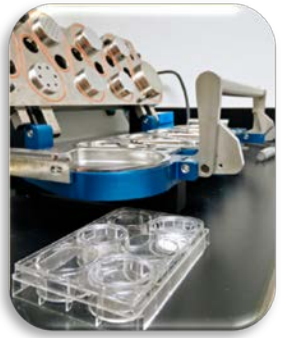
Realistic APSD: Summary

- **Realistic APSD as part of alternative BE approach can provide a *better prediction of deposition of inhaled particles in the lungs and capture patient variability* compared to current compendial methods of innovator products and generics**
- **Realistic APSD is currently part of alternative approach for solution MDIs (e.g., BDP MDI)**
  - Research demonstrates importance of extension of realistic APSD for suspension MDIs and DPIs, and be evaluated specifically for each generic drug product in comparison to the RLD.
    - Results dependent on ***methodology, dosage form, MT models chosen, and IPs***
  - ***MT models* and a *realistic range of inhalation profiles* can be used to compare the likely aerosol performance properties of OIDPs in the clinic**
    - ***MDIs – selection of MT models (include small and large models) is critical***
    - ***Suspension MDIs may be more sensitive to variations in MT models compared to solution MDIs***
    - ***DPIs – IPs appear to be critical***
  - Firms should submit pre-ANDA product development meeting to discuss scientifically justified realistic APSD proposals specific to the generic drug product of interest in comparison to the RLD

Dissolution: Overview

- **Dissolution as part of the alternative BE approach:**
  - Understanding how API dissolves at site of action for absorption once deposited
  - Predictive in vitro drug dissolution tests may provide a link between ***regional drug deposition and local/systemic pharmacokinetics*** for OIDPs
  - ***in vitro-in vivo relationships*** of OIDPs
    - formulation changes impact BA at site of action
- **Dissolution method is recommended to be**:
  - ***validated***, ***discriminatory***, and ***reproducible***





Grant 1U01FD004950-01 [FDA]
Sakagami, M., et al. *Pharmaceutical research* 36.7 (2019): 95.
Rohrschneider, Marc, et al. " *Molecular pharmaceutics* 12.8 (2015): 2618-2624.

Dissolution of OIDPs: Key Features

Sample Collection

- Aerosolized Fraction
  - DUSA
  - Ex-throat fraction (using MT model and filter)
  - Cascade impactors (NGI, FSA, ACI)
  - ADC system
- Dosing (# actuations)

Dissolution Apparatus

- USP Apparatus V (Paddle-over-disk)
- Diffusion-controlled apparatus
  - Transwell® insert/dish
- Flow through system
  - Flow through cell
  - Franz® diffusion cell

Dissolution Media

- Simulated lung fluid (SLF)
- Buffer
- Amount/type of surfactants
  - SDS
  - Tween

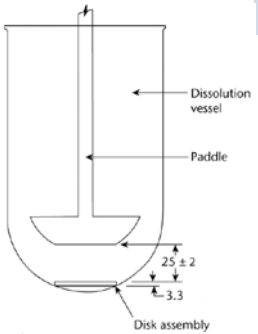
Method Validation

- Predictability
  - Correlation between formulation factors, dissolution, in vivo performance
- Discriminatory capability

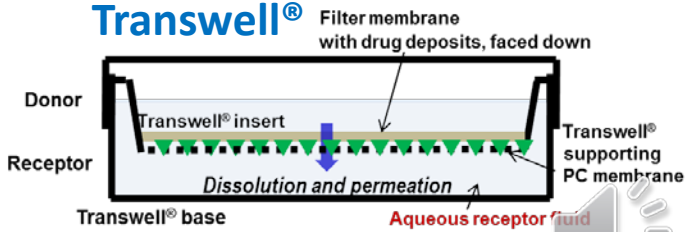
BE assessment

- Model entire dissolution profile
- Choose appropriate statistical analysis
  - Model independent or dependent

USP



Transwell®

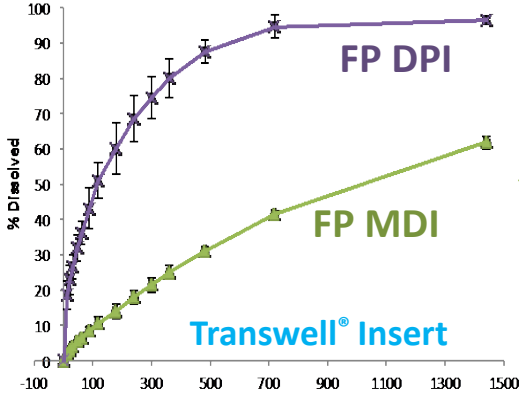


DUSA: Dosage Unit Sampling Apparatus
FSA: Fast Screening Anderson
ACI: Anderson Cascade Impactor
ADC: Aerosol Dose Collection
SDS: sodium dodecyl sulfate

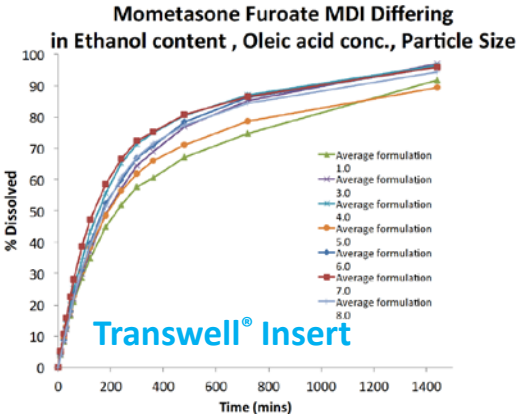
USP <724>Drug Release; USP-NF: https://online.uspnf.com/uspnf
Sakagami, M., et al., , *Pharmaceutical research* 36.7 (2019): 95.
https://collaboration.fda.gov/p4x8n2ijonv/
Price, Robert, et al. The AAPS Journal 22.2 (2020): 1-9.

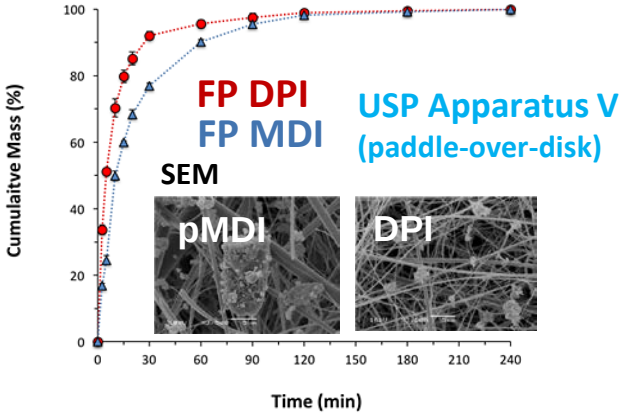
Dissolution and Formulation Differences

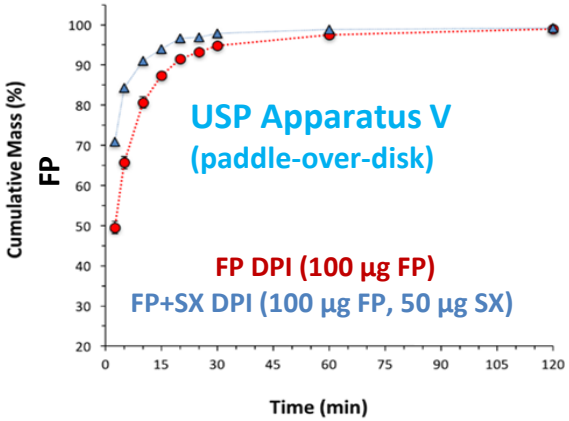
- ***In vitro dissolution is able to capture differences in formulations***



- ***MDI vs DPI***
- ***API particle size and excipient differences***
- ***Absence/presence of API***





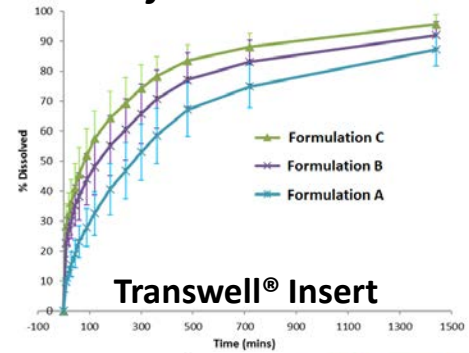


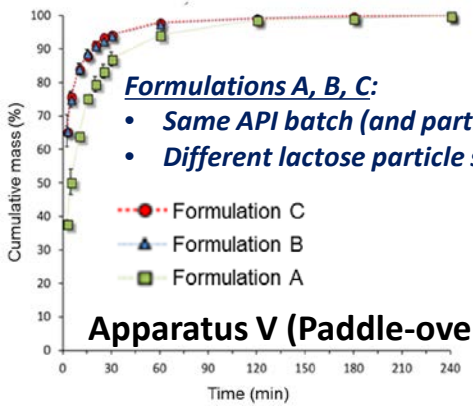
FP: Fluticasone Propionate,
SX: Salmeterol Xinafoate

Grants: 1U01FD004953 [FDA]; 1U01FD004950-01 [FDA]; 5U01FD004943 [FDA]
https://collaboration.fda.gov/p4x8n2ijonv/ - Günther Hochhaus, PhD.
Price, Robert, et al. *The AAPS Journal* 22.2 (2020): 1-9.

Dissolution and PK

FP DPI formulations

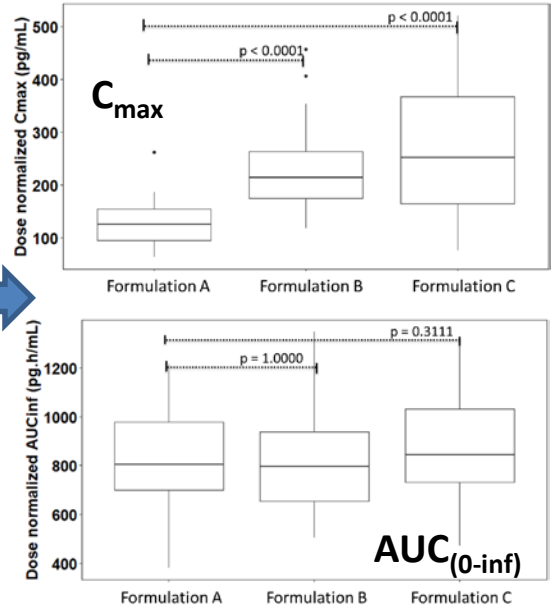




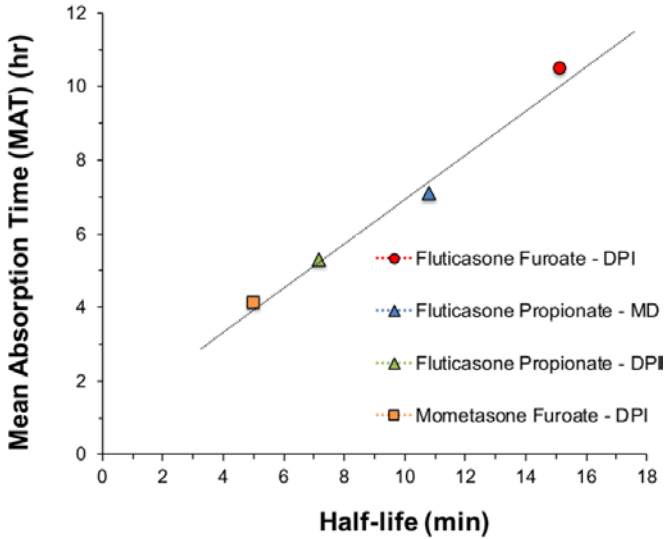
Formulations A, B, C:

- ***Same API batch (and particle size)***
- ***Different lactose particle sizes***

- ***Potential for correlating dissolution to systemic PK***



- ***Link between dissolution and systemic PK C_{max} and $AUC_{(0\text{-}inf)}$***



- ***Link mean absorption time (MAT) from PK measurements and dissolution half-life ($t_{0.5}$)***

AAPS ePoster Library. Boc S. 11/04/19; 280582; M0930-01-02; https://collaboration.fda.gov/p4x8n2ijonv/; Price, Robert, et al. The AAPS Journal 22.2 (2020): 1-9.

Dissolution: Summary

- **Dissolution as part of the alternative BE approach for OIDPs:**
  - Understand how API dissolves at site of action for absorption once deposited
  - Provides a link between regional drug deposition and local/systemic PK for OIDPs
  - ***in vitro-in vivo relationships*** of OIDPS (formulation changes impact BA at site of action)
    - Discriminating between differences in formulation
    - Potential to correlate to PK parameters (C_{max}, $AUC_{(0\text{-}inf)}$); link between MAT from PK measurements and $t_{0.5}$
- **When developing dissolution methods, the key features to consider:**
  - ***Sample collection, dissolution apparatus, dissolution media, method validation, BE assessment***
  - Method is recommended to be ***validated***, ***discriminatory***, and ***reproducible***
  - **Recommend firms submit pre-ANDA product development meeting to discuss scientifically justified dissolution proposals specific to the generic drug product of interest in comparison to the RLD**

Conclusions

- **Establishment of BE for locally-acting OIDPs occurs through *weight-of-evidence approach***
- **Comparative CCEP, PK and in vitro BE all provide indirect evidence of equivalent local delivery**
- **Alternative Approaches to comparative CCEP or PD BE studies for OIDPs need to address:**
  - **The *relationship of systemic PK data to local levels of drug within the lung* (at site of action)**
  - ***In vitro-in vivo correlations***: Relationship between in vitro product performance to local lung deposition and absorption (clinical performance)
- **As part of the alternative BE approach, realistic APSD may provide a *better prediction of deposition of inhaled particles in the lungs* and *capture patient variability* for OIDPs**
  - Consider ***methodology, dosage form, MT models chosen, and IPs***
- **As part of the alternative BE approach dissolution methods may provide understanding on how API dissolves at site of action for absorption once deposited, and potentially build towards *in vitro-in vivo relationships* of OIDPs**
  - Consider ***sample collection, dissolution apparatus, dissolution media, method validation,*** and ***BE assessment***
- **Firms are *highly encouraged* to submit a pre-ANDA Product Development Meeting**
  - Approaches should be scientifically justified with a comprehensive, significant body of data, and evaluated as statistically meaningful as possible

Challenge Question #1

Which of the following statements is NOT true?

A. A weight-of-evidence approach to establish BE for OINDPs is comprised of in vitro BE studies, a PK BE study, and a CCEP/PD BE study, in addition to formulation sameness and device similarity

B. Quantitative methods and modeling are not applicable for alternative BE approaches to the CCEP/PD BE study

C. To capture patient variability, mouth-throat model selection (inclusion of S and L models) is important when characterizing MDIs by realistic APSD methods

D. Dissolution may be able capture differences in formulations and connect to differences seen in systemic PK parameters

Acknowledgements

- FDA/CDER/OGD/ORS
  - Sneha Dhapare, PhD
  - Denise Conti, PhD
  - Bryan Newman, PhD
  - Liangfeng Han, MD, PhD
  - Markham Luke, MD, PhD
  - Lei Zhang, PhD
  - Robert Lionberger, PhD
- FDA/CDER/OPQ/OTR/DCDA
  - Jason Rodriguez, PhD
  - Changning Guo, PhD
  - Nathan Reed, PhD
  - Anubhav Kaviratna, PhD
- FDA/CDER/OGD/OB
  - Kimberly Witzmann, MD
- FDA/CDER/OPQ/ONDPII/NDPB3
  - Renishkumar Delvadia, PhD

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Questions?

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Resources

- 21 CFR §320.23 Basis for measuring in vivo bioavailability (BA) or demonstrating bioequivalence (BE).
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- FDA product-specific guidance for Beclomethasone Dipropionate Inhalation Aerosol, Metered [RLD: QVAR Redihaler® (Posted May 2019)].
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- FDA draft guidance for industry: Formal Meetings Between FDA and ANDA Applicants of Complex Products under GDUFA.
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- New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products.