Overcoming Barriers to Entry for Complex Generic Oral Inhalation Drug Products

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Disclaimer

The opinions expressed in this presentation are those of the speaker and may not reflect the position of the U.S. Food and Drug Administration.

Determination of Generic Drug Product's Equivalence to its Reference Listed Drug

- Regulations require that applicants conduct testing using the most accurate, sensitive, and reproducible approach (21CFR320.24)
- The choice of methodology used for establishing and ensuring Therapeutic Equivalence throughout product's lifecycle will involve considerations for:
    - Formulation design
    - Product composition
    - Site of action
    - Mechanism of drug delivery and release
    - Ability to measure drug's availability at the site of action
    - Expected and measured therapeutic effects and their relationship to drug concentration
    - Other factors related to patient-product interaction

Inhalation Product Challenges

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4. *In vitro* studies are the most sensitive method for determining BE, but currently not reflective of what happens *in vivo*
5. Weight-of-evidence approach is cumbersome, comparative clinical endpoint studies are long, costly, and least sensitive to formulation differences

Complex Drug Products In GDUFA II

- Complex active ingredients- peptides, polymeric compounds, complex mixtures of APIs, naturally sourced ingredients
- Complex formulations/dosage forms- liposomes, colloids, transdermal, long-acting injectables
- Complex routes of delivery- locally acting drugs
- Complex drug-device combination products- nasal sprays, metered dose inhalers, dry powder inhalers
- Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement

GDUFA II commitment letter. http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Pre-ANDA Program for Complex Products Under GDUFA II

- Clarify regulatory expectations for prospective applicants early in product development
- Help applicants develop more complete submissions
- Promote a more efficient and effective review process
- Reduce the number of review cycles necessary to obtain ANDA approval of complex products

FDA Research Coordination for Inhaled Drugs

Formulation

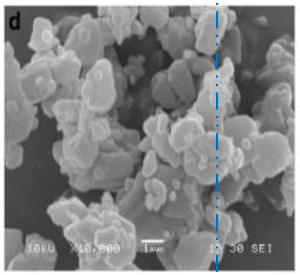
Device

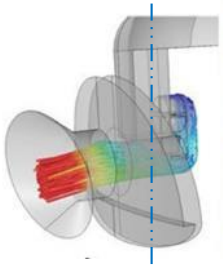
Human Factors

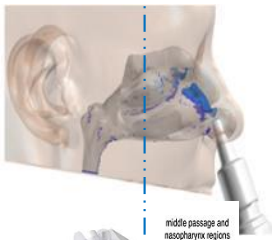
Regional Deposition

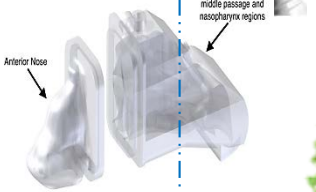
Dissolution

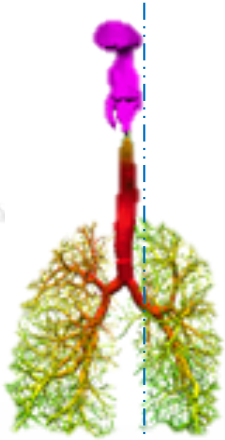
Absorption

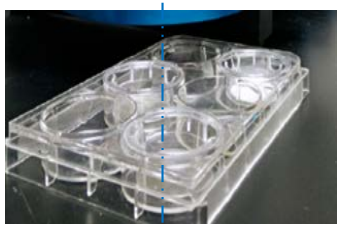


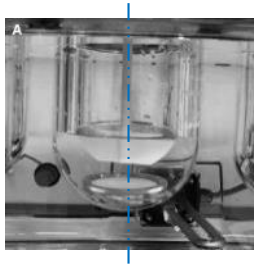


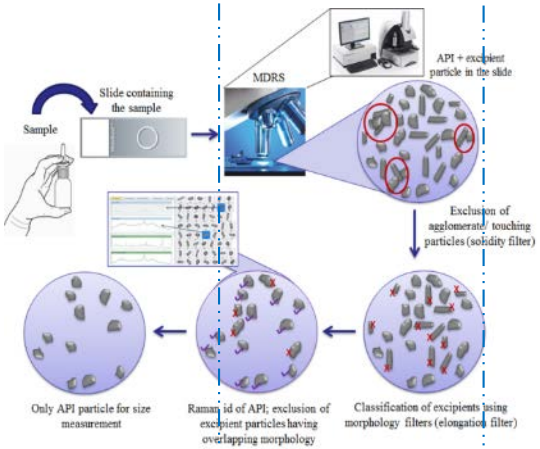


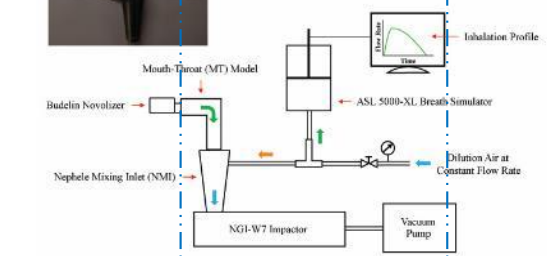


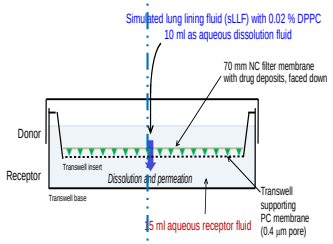












Orally Inhaled Drug Products: Weight-of-Evidence Approach

2013
No generic OIDP products;
1st product-specific guidance for OIDP published

Device and Formulation Design

Comparative In Vitro Studies

Comparative Pharmacokinetic Studies

Comparative Pharmacodynamics or Clinical Endpoint Studies

2017
>50% of all OIDPs have PSGs;
OIDP ANDA applications reviewed

Inhalation Product Challenges

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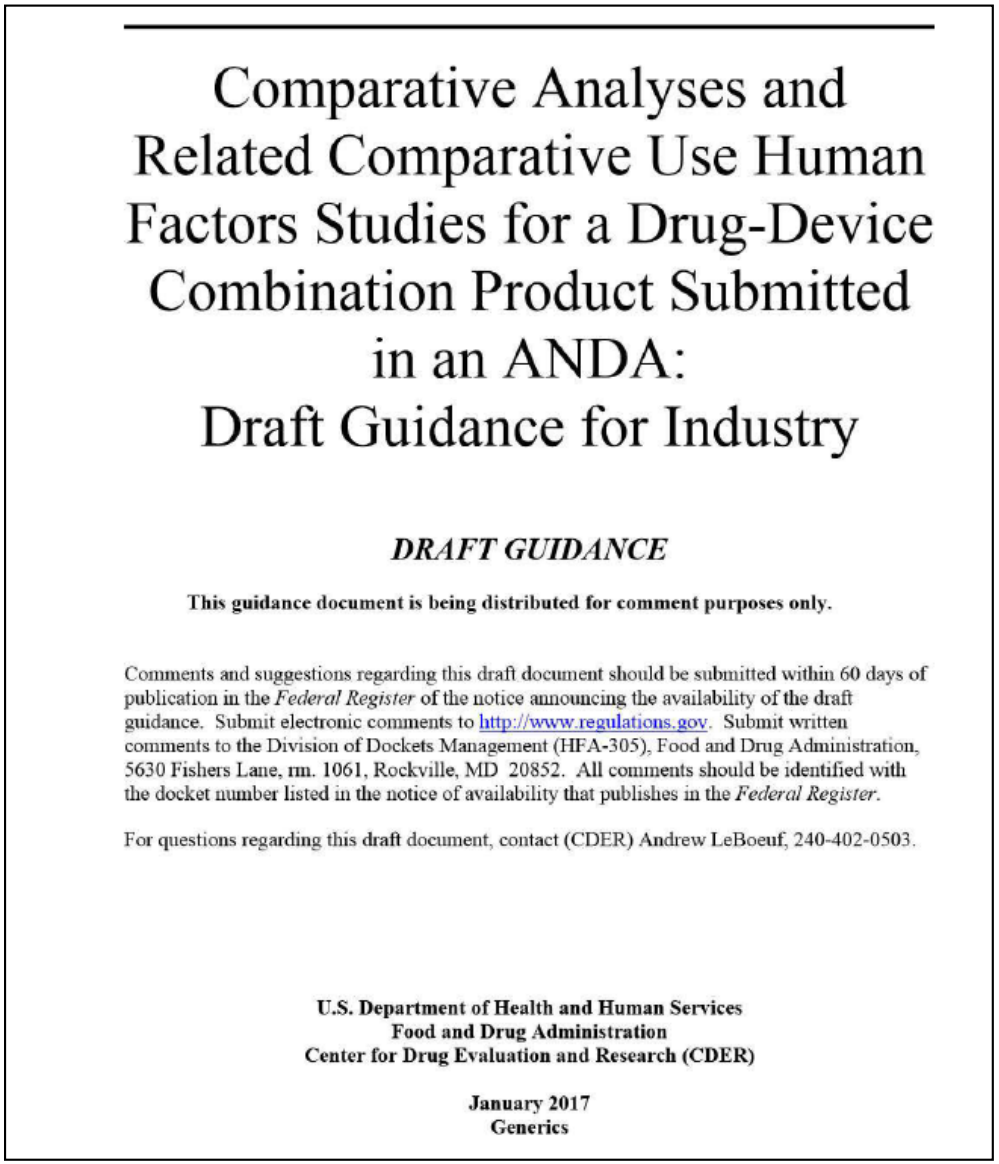
Drug-Device Combination Products

Generic Drug-Device Combination Products

- Therapeutically equivalent: can be substituted with the full expectation that the generic product will produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling
- Same expectation for generic drug-device combination products
- Generic and RLD do not need to be identical, as long as differences do not preclude approval under an ANDA
- FDA expects that end-users can use the generic combination product when it is substituted for the RLD without the intervention of the health care provider and/or without additional training prior to use of the generic combination product

Guidance



Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA:
Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Andrew LeBoeuf, 240-402-0503.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2017
Generics

Inhalation Product Challenges

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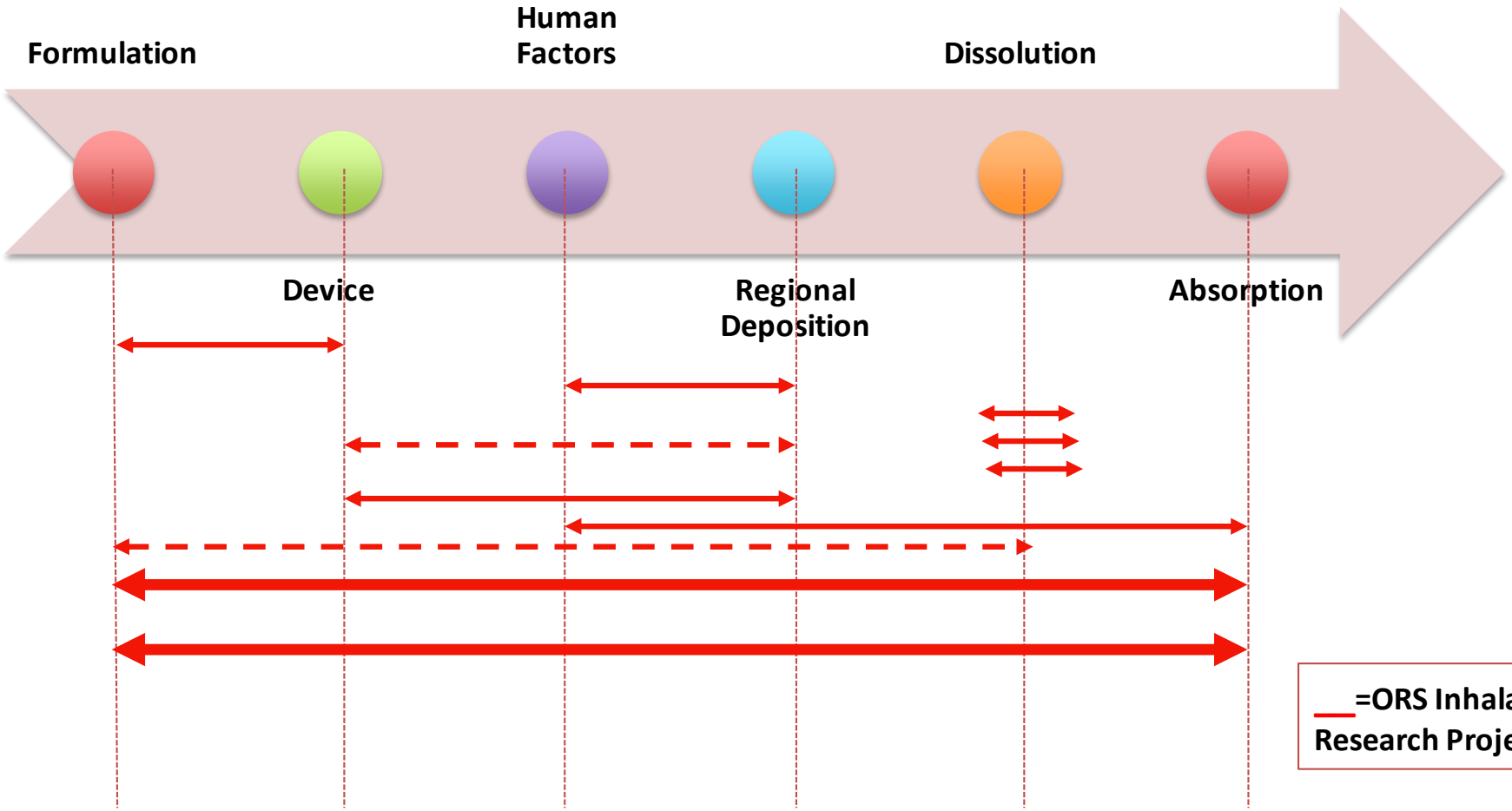
GDUFA Regulatory Science Projects for OIDPs



Comprehensive Evaluation of Formulation Effects on MDI Performance

- FY-13 grant # U01FD004943:
  - Awarded to Cirrus Pharmaceuticals (present: Recipharm)
  - Expanded to University of Florida

- This project investigates the effect of excipient concentrations on the aerosolization performance of typical hydroflouroalkane (HFA)-based MDI formulations and evaluate the sensitivity of the in vitro methods in detecting excipient concentration changes.

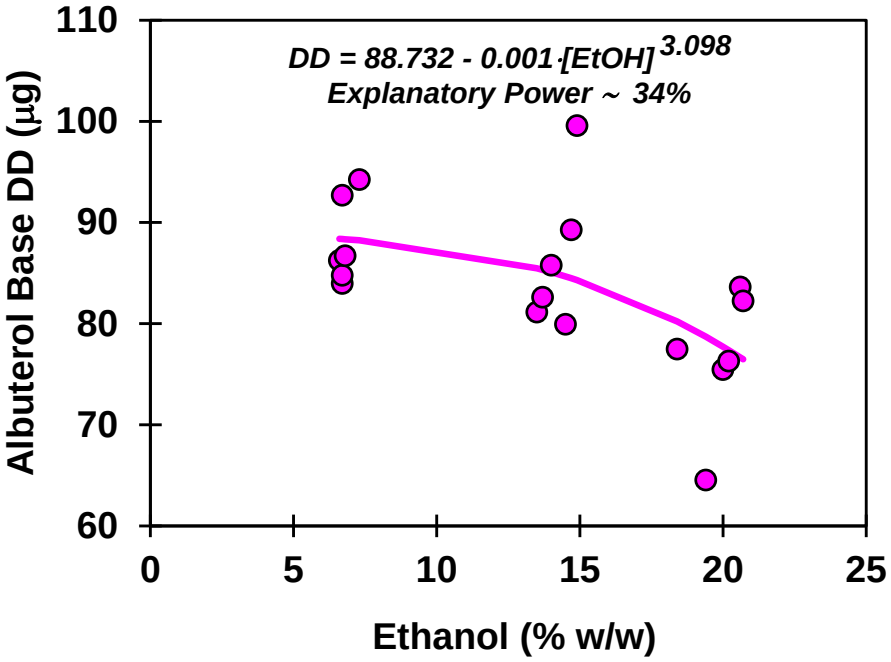
MDI Batch Manufacturing Plan

- The levels of excipients [ethanol (EtOH) and oleic acid (OA)] and drug PSD D50 were varied according to a reduced factorial statistical design of experiments (DOE) approach. The following ranges were studied:

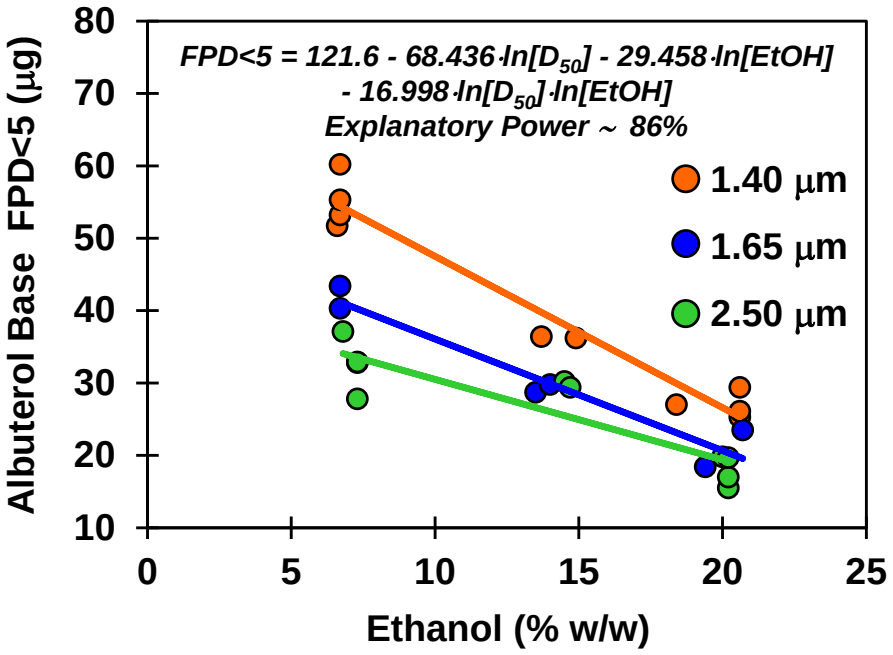
MDI Formulation	PSD D50 (µm)	EtOH (% w/w)	OA (% w/w)
AS suspension	1.4 – 2.5	7 – 20	0.005 – 0.1
MF suspension	1.1 – 2.0	0.45 – 3.6	0.001 – 0.025
BDP solution	N/A	7 – 9	0 – 2

Conti, D. S.; Holt, J.; Sheth, P.; Sandell, D.; Hickey, A.; Saluja, B. "The Effects of Formulation Factors on the Aerosolization Performance of Metered Dose Inhalers." In: AIChe Annual Meeting, 2016, San Francisco, CA, United States. Poster presentation

Albuterol Sulfate Suspension

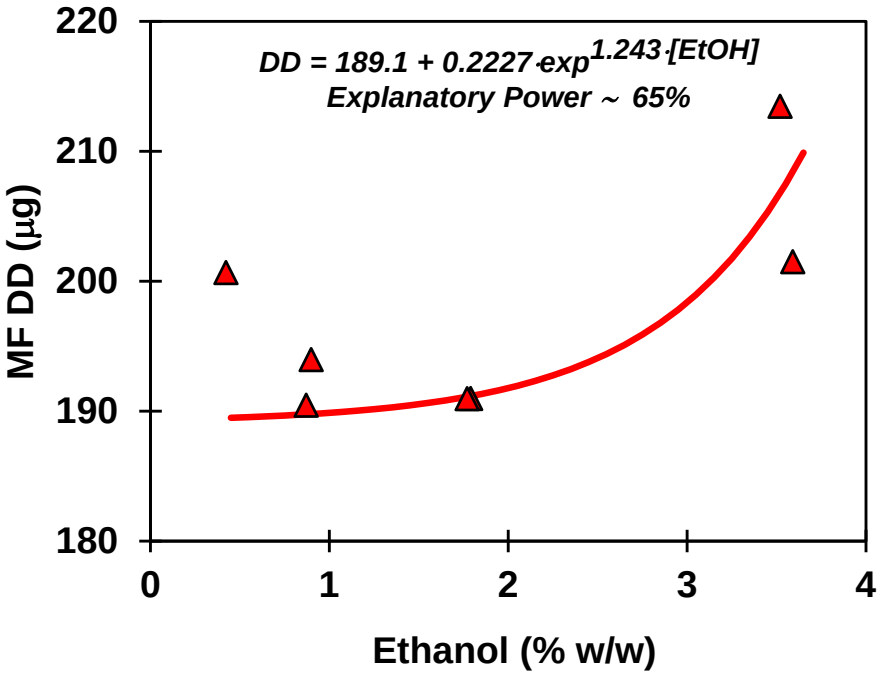


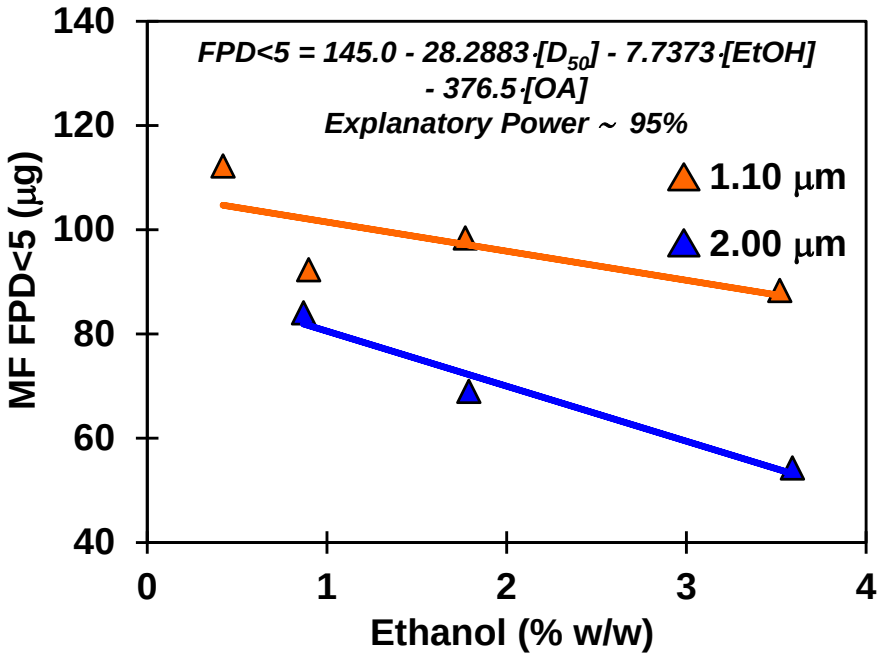
As the level of ethanol increased from 7% to 20% w/w, the DD of albuterol decreased by 13%.



As the level of ethanol increased from 7% to 20% w/w, the FPD<5 of albuterol decreased by 51% (1.40 µm), 50% (1.65 µm) and 45% (2.50 µm).

Mometasone Furoate Suspension

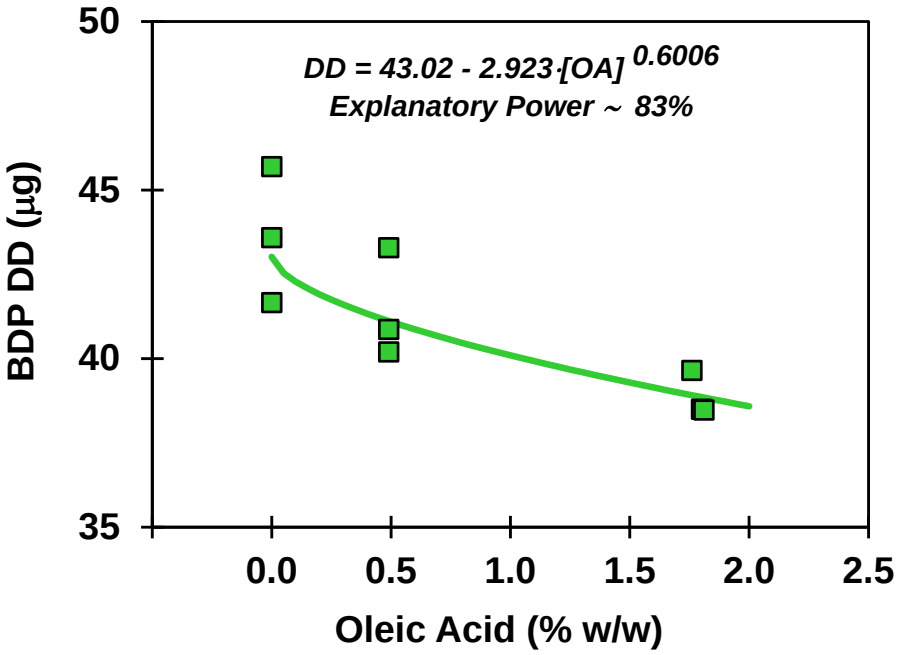


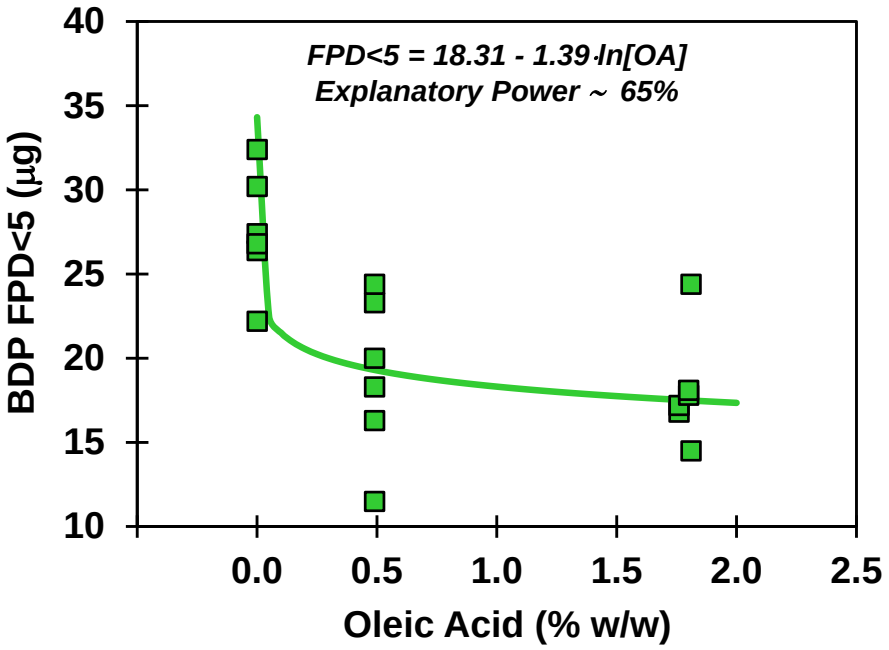


As the level of ethanol increased from 1.8% to 3.6% w/w, the DD of MF increased by 9%.

As the level of ethanol increased from 0.45% to 3.6% w/w (1.1 µm) and from 0.90% to 3.6% (2.0 µm), the FPD<5 of MF decreased by 21% and 35%.

Beclomethasone Dipropionate Solution





As the level of oleic acid increased from 0% to 2% w/w, the DD of BDP decreased by 11%.

As the level of oleic acid increased from 0% to 2% w/w, the FPD<5 of BDP decreased by 34%.

Research Conclusions

- The changes in API PSD had statistically significant effects on the APSD performance of suspension MDI formulations studied, but not on DD.
- The changes in concentrations of excipients (ethanol and oleic acid) showed, in some cases, statistically significant effects on DD and APSD performance of suspension and solution MDI formulations studied. However, several cases without effects were also found, despite some large changes in concentrations of inactive ingredients studied.
- The possible effects of varying these characteristics must be studied on a case-by-case basis.

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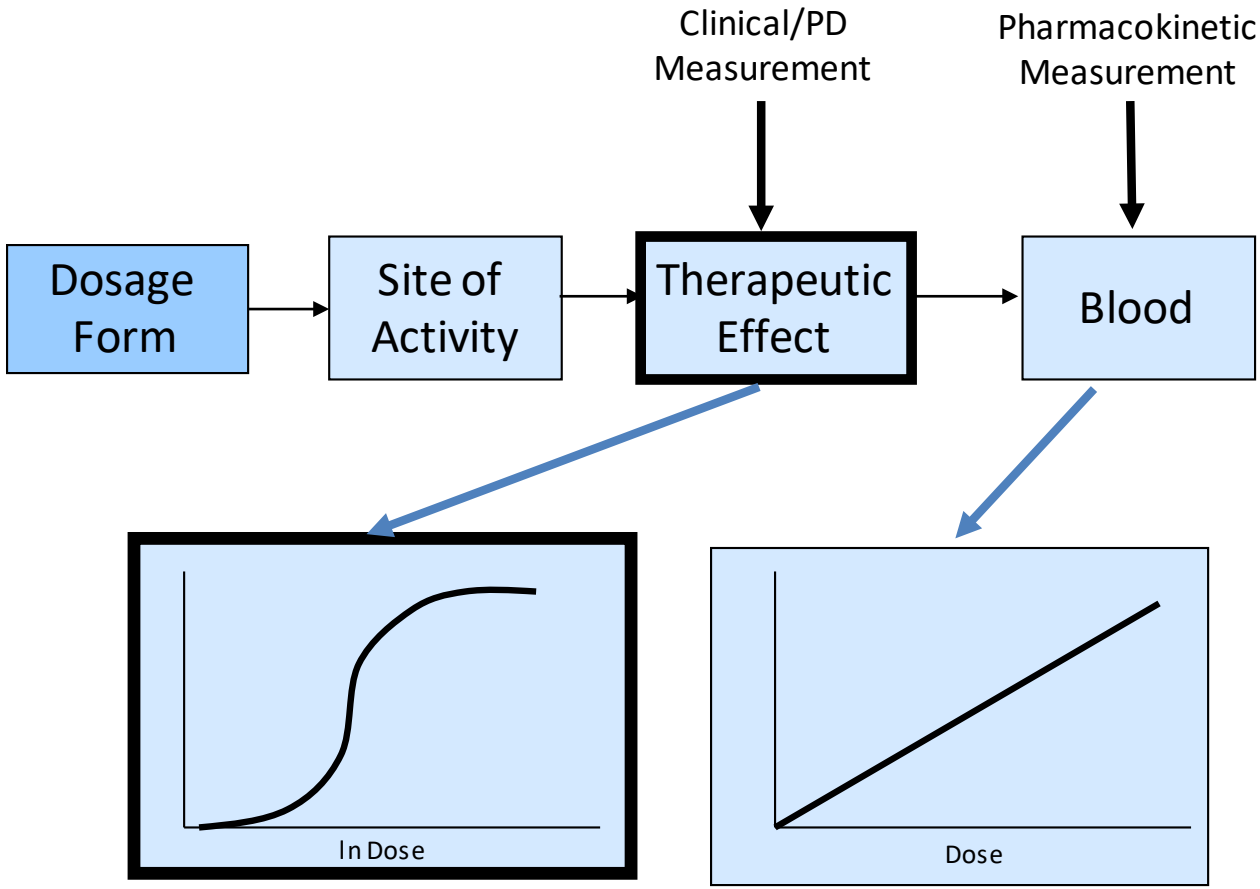
BE for Locally-Acting Drugs

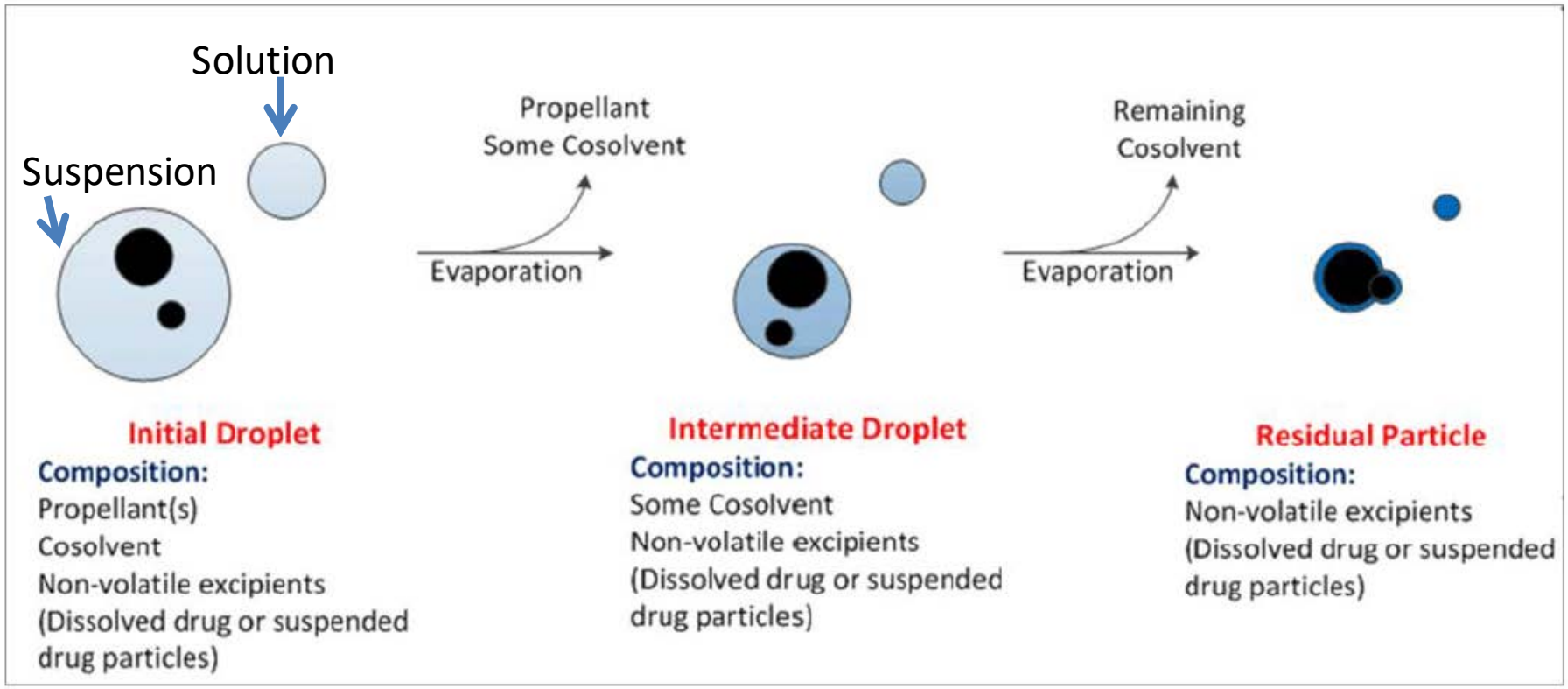


- Not intended to be absorbed into the bloodstream
- Delivered directly to sites of action (lung)

Products Delivered to the Respiratory System

- Orally inhaled drug products
- Factors influencing patient-product interactions and drug bioavailability include:
  - dose percent deposited in the lungs vs. dose percent swallowed and absorbed from the GI tract
  - local solubility/permeability
  - receptor affinity
  - deposition in central vs. peripheral parts of the pulmonary tree
  - pulmonary residence time
  - local clearance (mucociliary transport and RES uptake)
  - device design
  - effects of formulation differences on product performance

Current Challenges: How do solution MDIs reach the lung site of action?



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Clinically Relevant In Vitro Performance Test

- Research grant # U01FD005231 awarded to Virginia Commonwealth University (VCU) in 2014

- Goal: To determine whether **realistic physical mouth-throat models** provide better in vivo predictability to characterize aerodynamic particle size distribution (APSD) of orally-inhaled drug products (OIDPs)

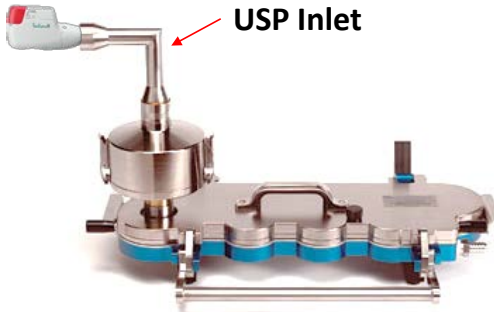
Why should we perform more realistic APSD in vitro tests for OIDPs?

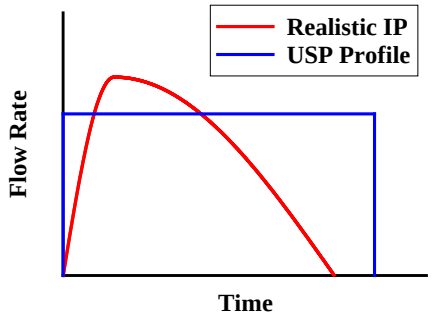
- APSD defines where the particles are likely to be deposited following inhalation
  - 1 - 5 μm: Lungs
  - > 5 μm: Oropharynx and swallowed
  - < 1 μm: Exhaled
- Current in vitro methods for APSD determination are designed for **quality control** and may not be predictive of deposition in vivo
- USP inlet and inhalation profile are **less predictive** and do not account for variability

Andersen Cascade Impactor (ACI)

Next Generation Impactor (NGI)

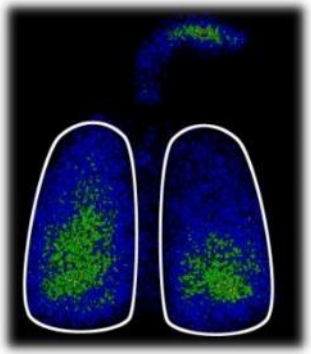
http://www.copleyscientific.com/downloads/brochures





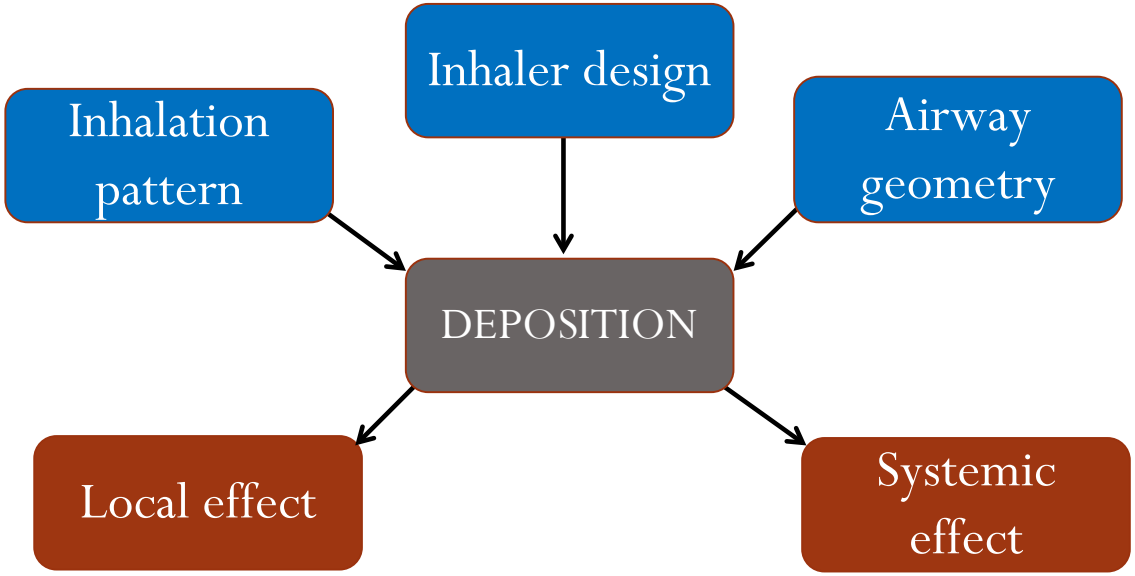
Why should we perform more realistic APSD in vitro tests for OIDPs?

- In vivo imaging methods (e.g., Gamma scintigraphy) are expensive and expose patients to radiation



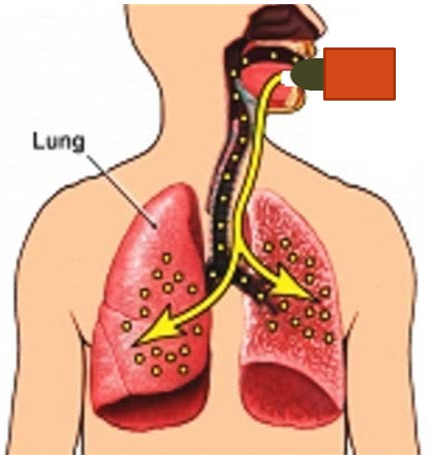
http://www.flowcaps.com/trial.htm

- Several factors influence the fate of inhaled medication



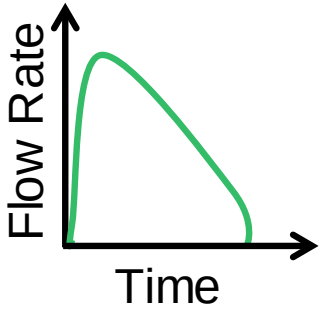
Clinically Relevant APSD In Vitro Test

A **more realistic in vitro APSD method** is important for pharmaceutical development and quality control of OIDPs

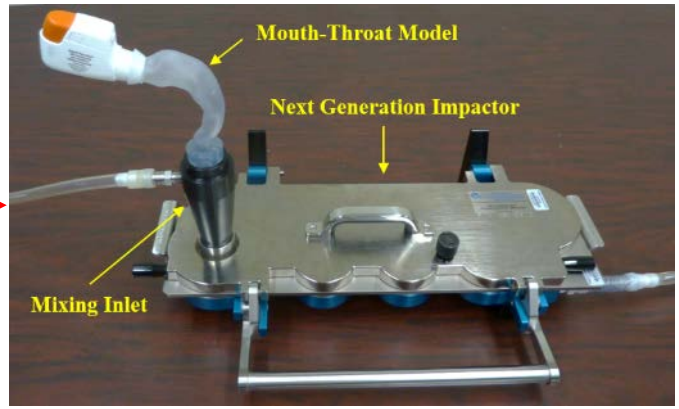


http://images.lifescript.com/images/ebsco/images/inhaled_poison.jpg

Physical mouth-throat (MT) models



Representative inhalation profiles (IP)

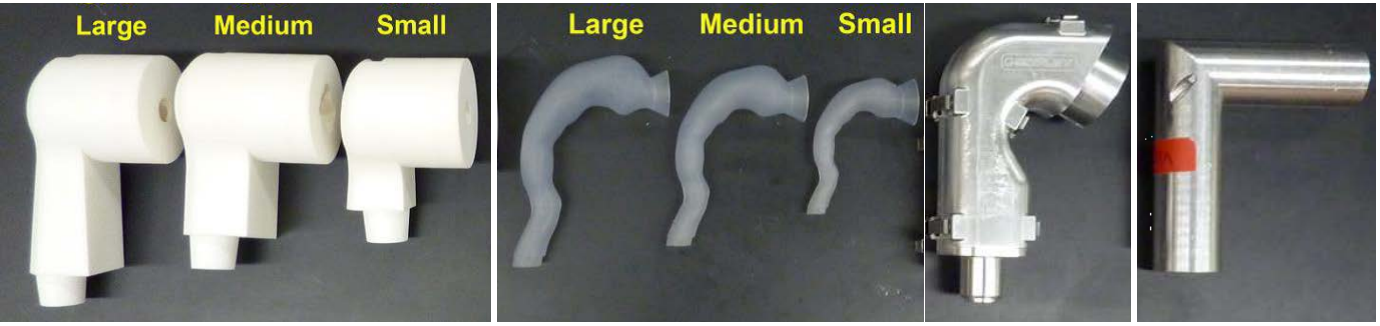


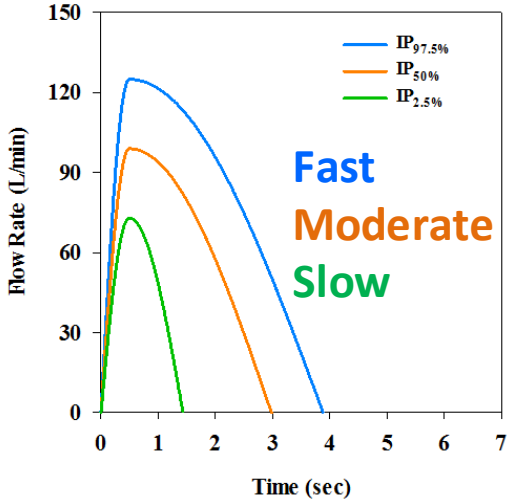
In vitro APSD method more predictive of in vivo deposition

Study Variables

Various **realistic MT models** coupled with **representative IPs**

OPC **VCU** **AIT** **USP**





https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm503040.htm

Different inhalers based on availability of flow rate information and in vivo scintigraphy deposition data

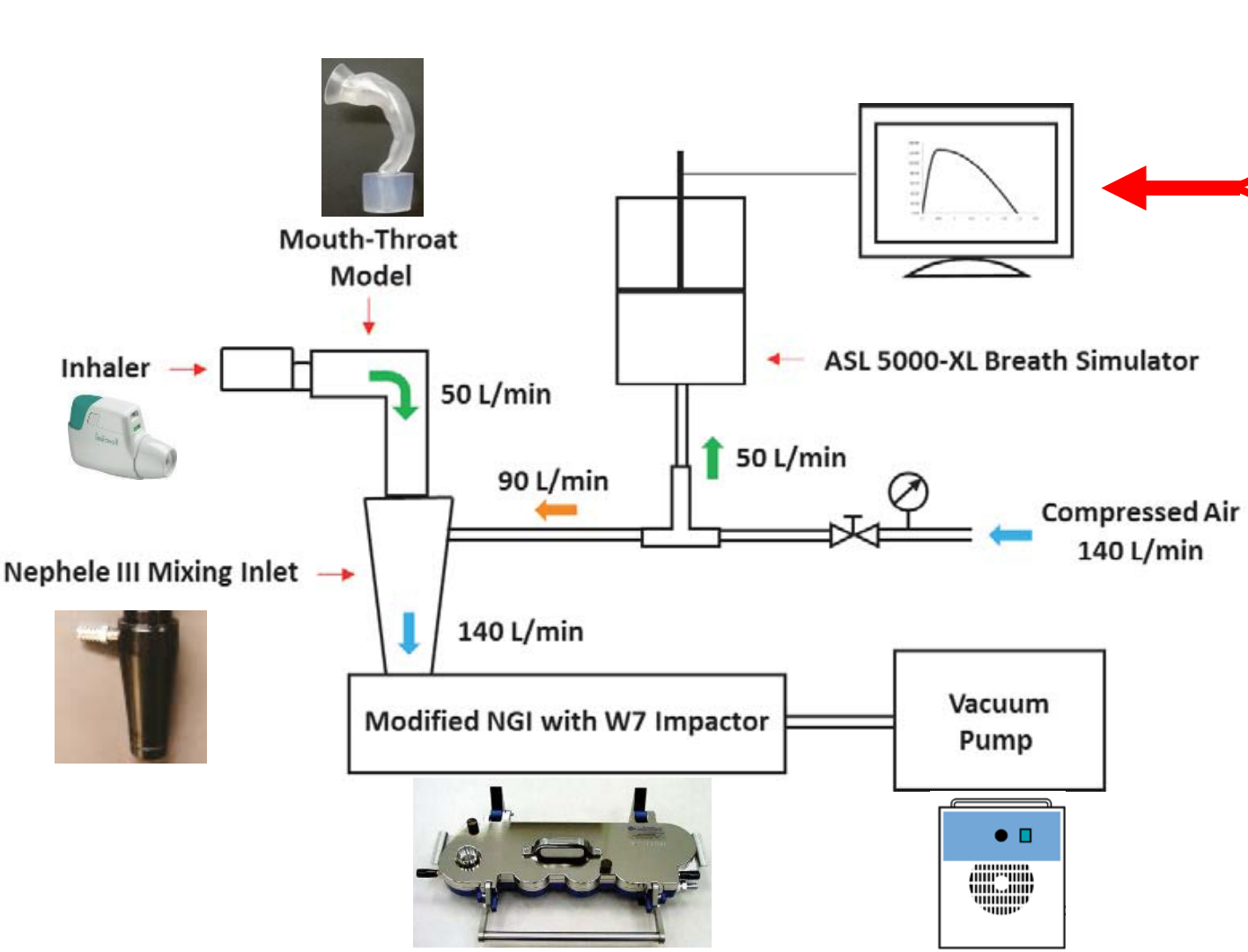
*Budesonide Dry Powder Inhaler (DPI)

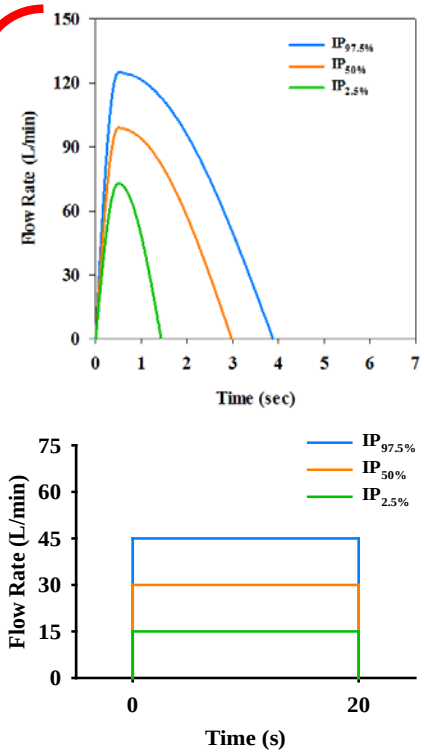
Albuterol Metered Dose Inhaler (MDI)

*Fenoterol Inhalation Spray

* Products not approved in the US, but commercially-available in Europe.

Experimental Set Up



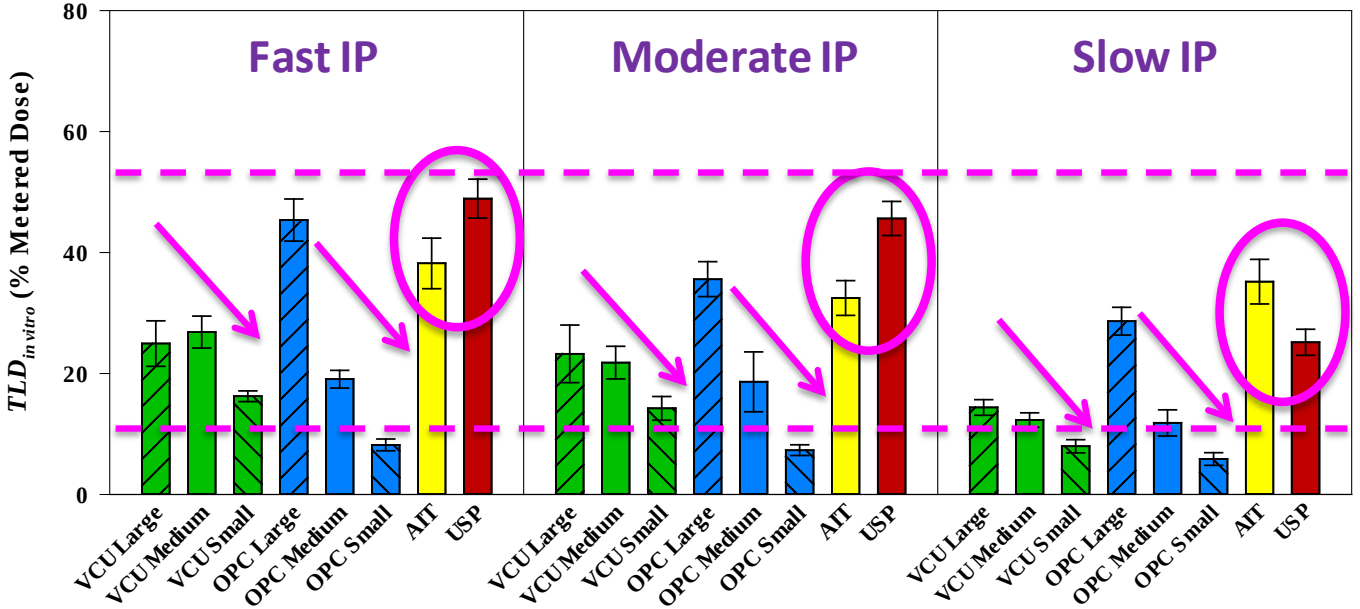


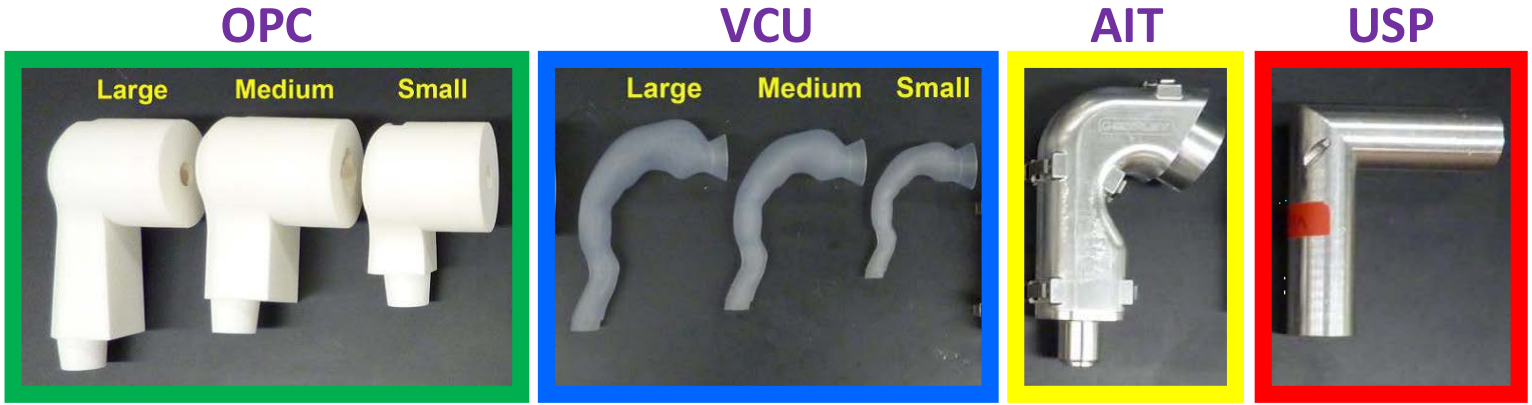
Fast
Moderate
Slow

Courtesy of Dr. Renish Delvadia, Ph.D. (FDA/OGD/ORS)

MDI Results

The in vitro performance of the MDI depends on both the realistic MT model and representative Inhalation Profile

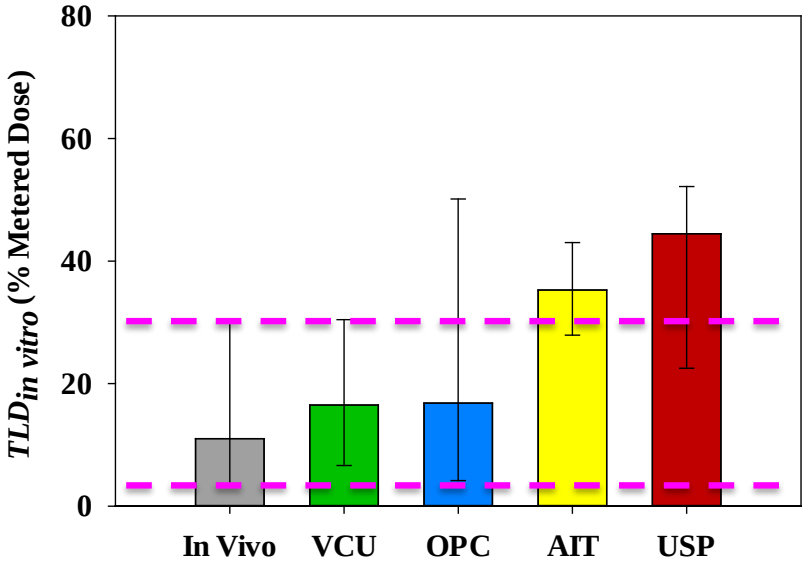


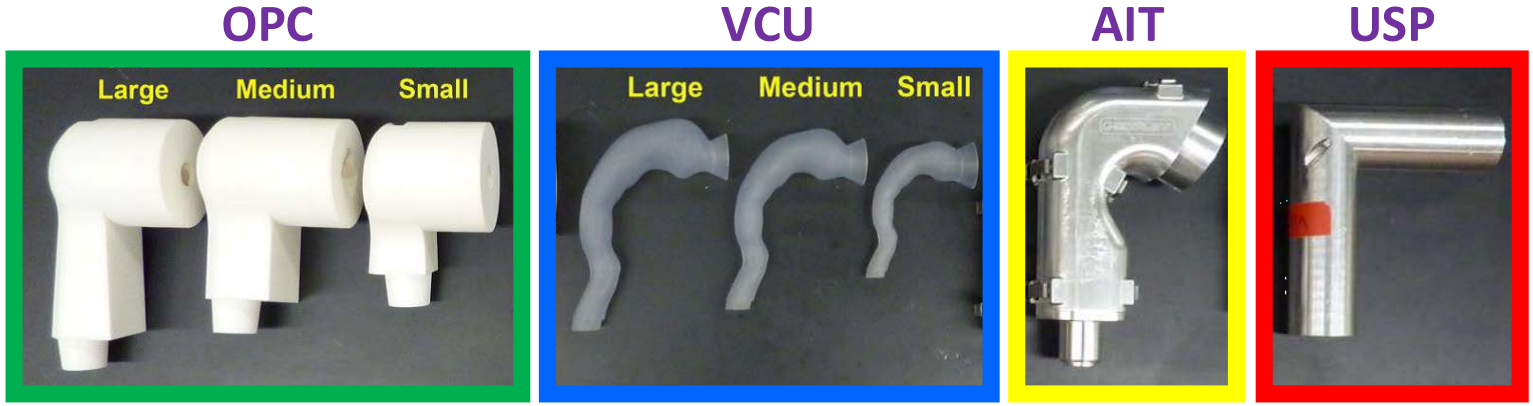


MDI Results

In vitro - in vivo total lung deposition (TLD) comparison

- VCU and OPC: good prediction
- AIT and USP: over-prediction

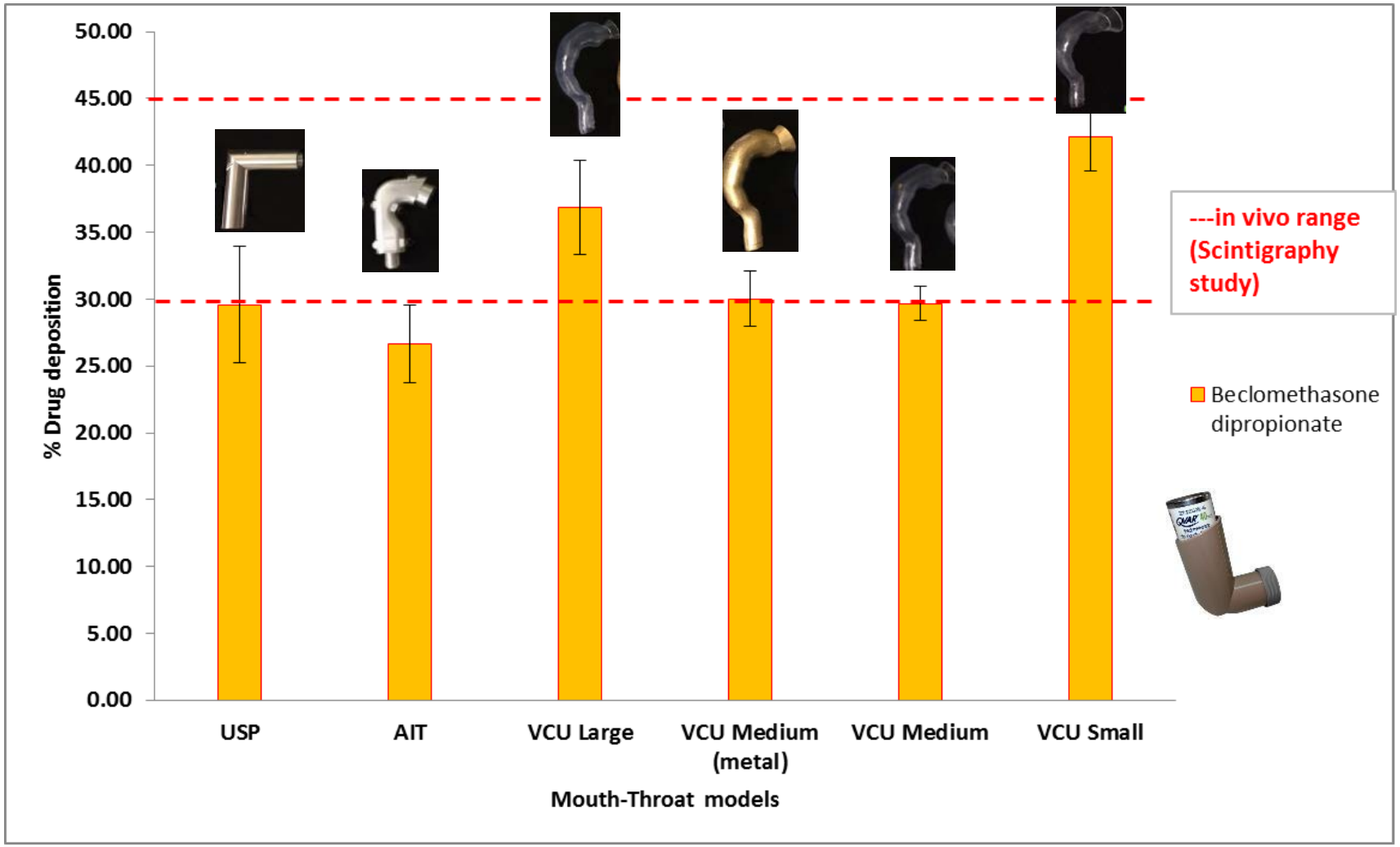




Research Conclusions

- A more realistic APSD in vitro test for OIDPs provides a **better prediction** of where inhaled particles may be deposited in the lungs compared to the current APSD in vitro test which uses the USP inlet
- Importance for **generic** OIDPs
  - Product development
  - Quality control
  - Faster, less expensive and more sensitive method compared to clinical endpoint bioequivalence studies

Current Challenge: Clinically Relevant Mouth-Throat Models



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Pharm Res
DOI 10.1007/s11095-017-2235-y

RESEARCH PAPER

Predicting Pulmonary Pharmacokinetics from *In Vitro* Properties of Dry Powder Inhalers

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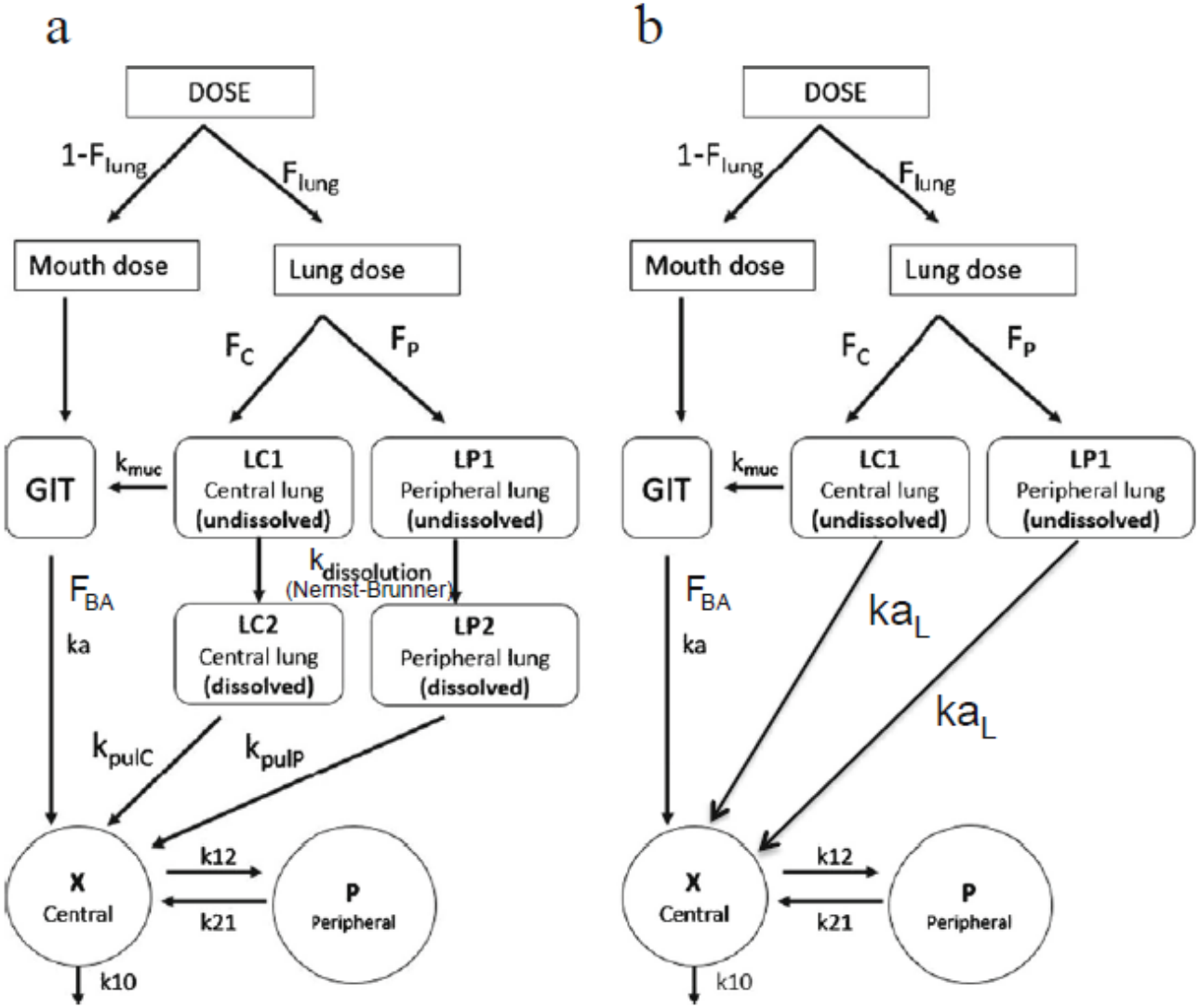
ABSTRACT

Purpose The ability of two semi-mechanistic simulation approaches to predict the systemic pharmacokinetics (PK) of inhaled corticosteroids (ICSs) delivered via dry powder inhalers (DPIs) was assessed for mometasone furoate, budesonide and fluticasone propionate. ... providing a significant advantage over approach 2 with regard to accuracy of *in vivo* predictions.

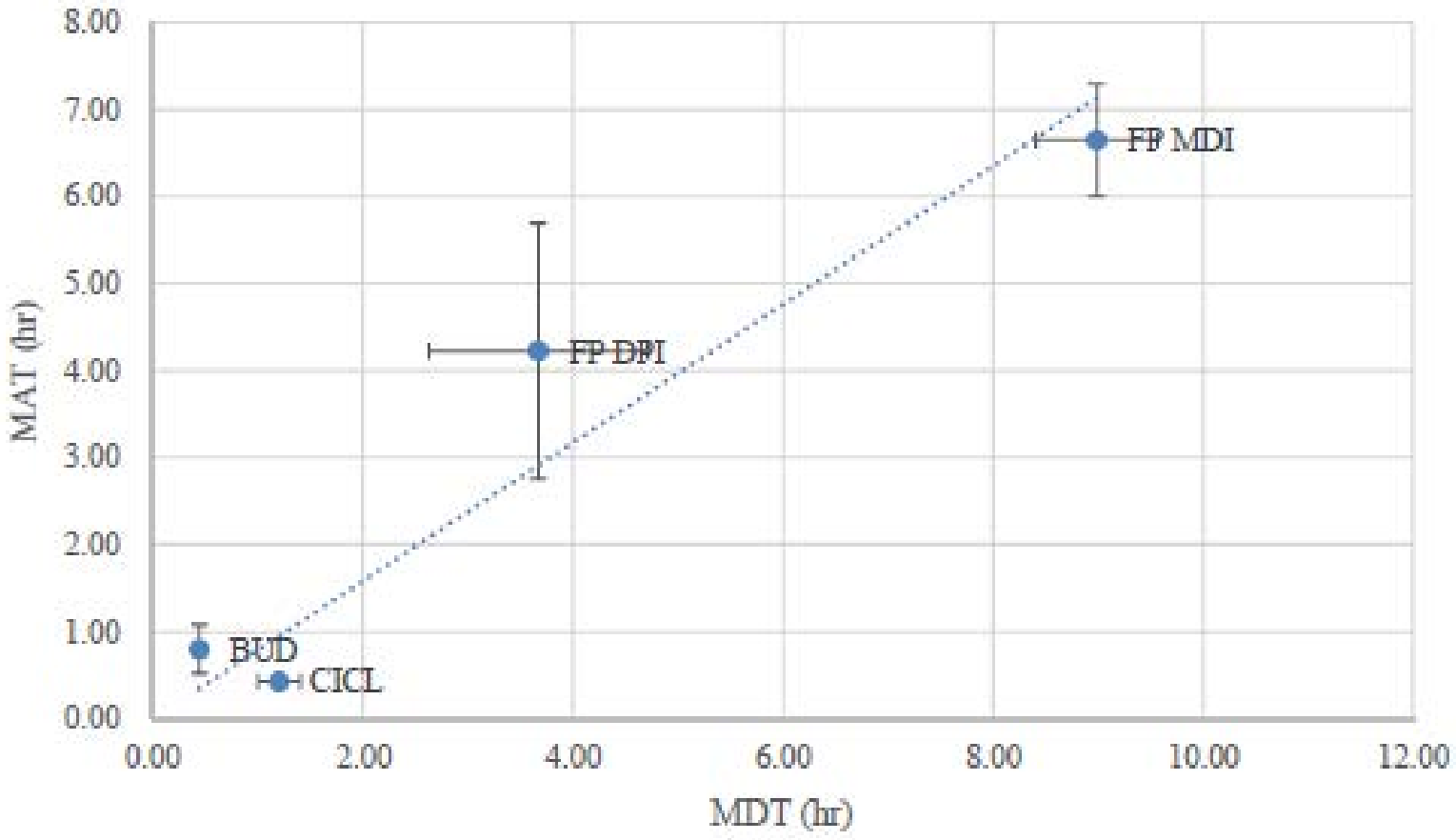
KEY WORDS dissolution · inhalation · inhaled corticosteroids · *in vitro/in vivo* · solubility

Predictive Models of Regional Lung Deposition



Bhagwat, S., Schilling, U., Chen, MJ. et al. Pharm Res (2017). https://doi.org/10.1007/s11095-017-2235-y

Correlation: Mean Dissolution Time (measured) and Mean Absorption Time (Literature)



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Conclusions

- OIDPs have a number of complex challenges
  - Complex Dosage forms (device)
  - Formulation changes
  - PK is downstream of the site of local action
  - Lack of *in vitro* to *in vivo* correlations
  - Comparative clinical endpoint study challenges
- Research conducted under the GDUFA Regulatory Science Program is addressing these challenges
- Goals are to
  - Develop new tools to evaluate drug equivalence and support drug development
  - Promote a more efficient and effective review process
  - Reduce the number of review cycles necessary to obtain ANDA approval of OIDPs


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