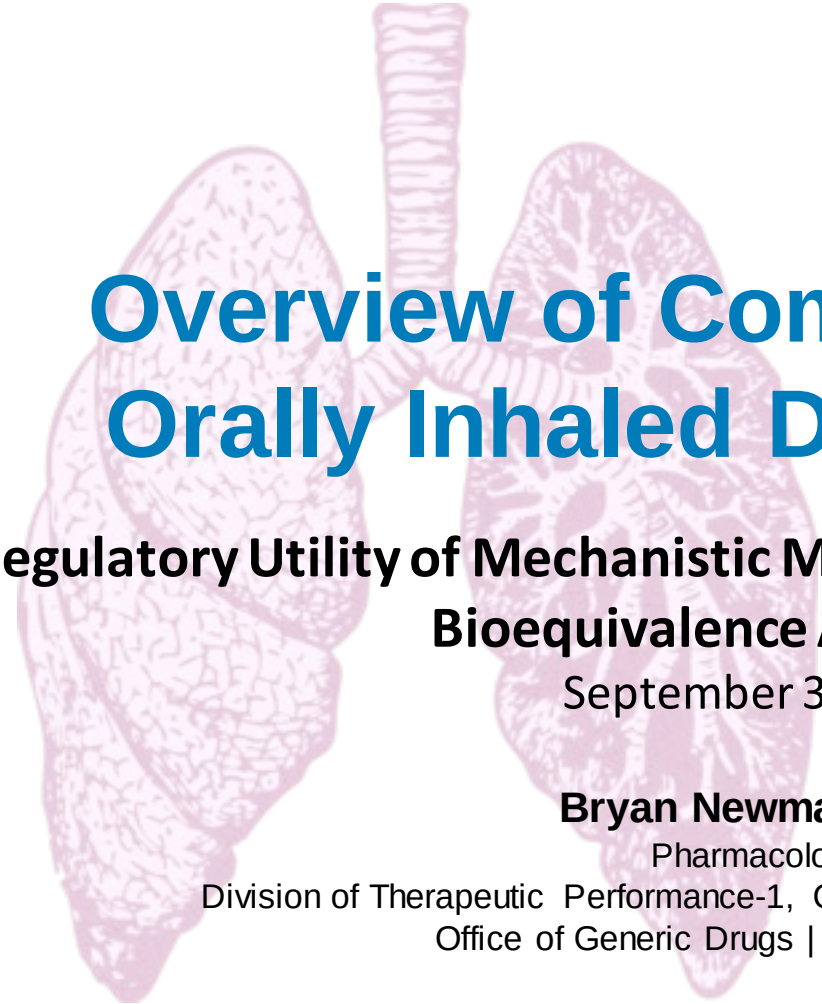

U.S. FOOD & DRUG ADMINISTRATION

Overview of Complex Generic Orally Inhaled Drug Products

Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

September 30, 2021

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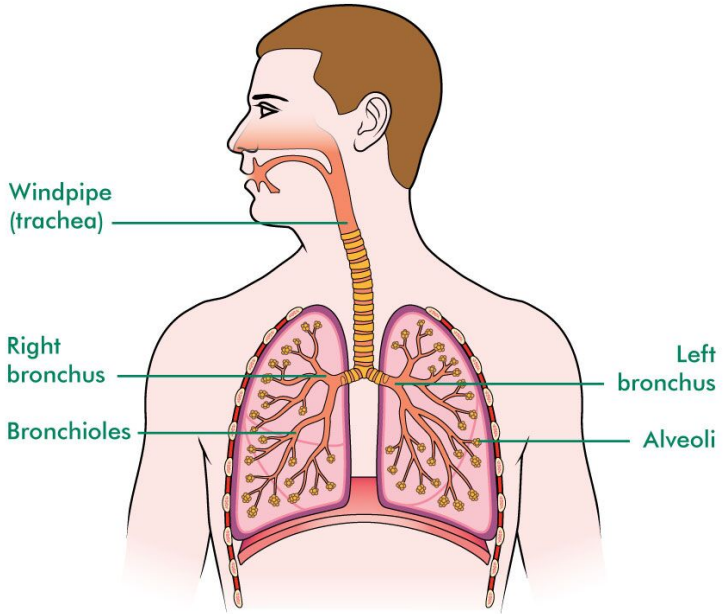
Outline

- Discussion on respiratory system, its diseases and treatment methods
- Complexity of orally inhaled drug products and methods for establishing bioequivalence (BE)
- Recent advancements and alternatives for establishing BE

Basics of the Respiratory System

- Three regions:
  - Upper (extrathoracic)
    - Heat / humidify incoming air
  - Conducting (tracheobronchial)
    - Weibel generations 0 to 16
    - Contain smooth muscle
    - Epithelium contains many cell types, some of which are ciliated and mucus secreting to facilitate mucocilliary clearance of foreign particles
    - Airway volume approximately 150 mL
  - Alveolated (respiratory)
    - Weibel generations 17 to 23
    - Site of gas exchange
    - Surfactant secreting cells present
    - Surface area approximately 50 – 100 m^2
    - Volume of alveolar region between 2.5 to 3 L



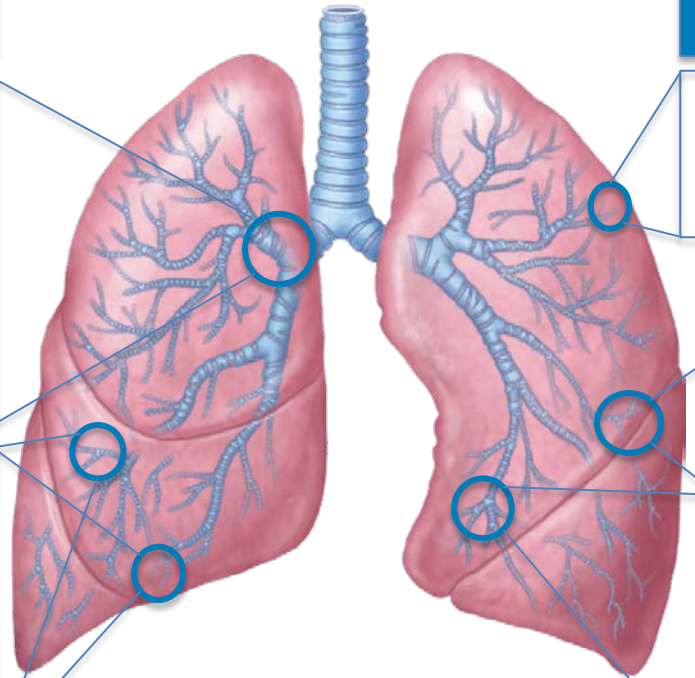
https://www.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/77-50037/macd024-respiratory-system-labelled-20190613

Respiratory Diseases

Obstructive Diseases

Asthma
- Airway hyperresponsiveness and inflammation
- Bronchial constriction with hypertrophied smooth muscle and bronchial wall edema
- Mucus gland hypertrophy with increased mucus production

Chronic Obstructive Pulmonary Disease
- Chronic bronchitis – small airway constriction with excess mucus production
- Emphysema – disruption of alveolar space and/or membrane



Restrictive Diseases

Pulmonary Fibrosis
- Alveolar wall thickening and scarring
- Loss of elasticity

Other Diseases

Respiratory Infections
- Inflammation of parenchyma with immune cells

Cystic Fibrosis
- Hypertrophied mucus glands with excessive mucus production
- Impaired mucociliary clearance
- Mucus plugging of small airways
- Chronic infections

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Demographics and Impacts from Respiratory Diseases

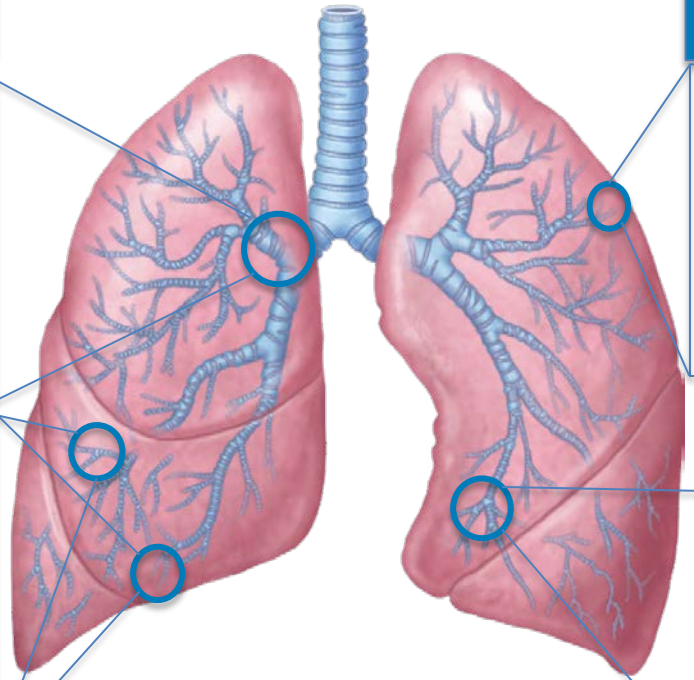
Obstructive Diseases

Asthma [1,2]

- Typical age range: All ages
- Gender: higher in boys than girls (age<18); higher in women than men (age>18)
- Cost to Americans: > $80 billion annually

Chronic Obstructive Pulmonary Disease [3,4]

- Typical age range: Often diagnosed between 30-40 years of age and older, though younger is possible
- Gender: higher in women than men
- Cost to Americans: projected to be ~ $49 billion in 2020



Restrictive Diseases

Pulmonary Fibrosis [5,6,7]

- Typical age range: much more likely in middle-aged to older adults:
- Gender: more likely in men than women:
- Cost to Americans: ~ $2 billion annually, excluding medication costs

Other Diseases

Cystic Fibrosis [8]

- >30,000 diagnosed in the U.S.
- Typical age range: diagnosed as early at 2 years of age and older
- Gender: occurs about equally
- Costs to Americans: highly variable depending on treatment

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Treating Respiratory Diseases

- The inhalation route of administration is often the preferred method for treating respiratory diseases, since it provides a direct path for drug delivery to airway surfaces:
  - Faster onset of action than oral administration
  - Smaller dose can be effective
  - Minimizes unwanted side effects from systemic exposure
  - Avoids drug loss due to first pass metabolism from liver
  - Provides another option for systemic drug delivery
- Reaching the lung site of action requires:
  - Aerosolization of the drug
  - Aerosol particle size distribution (PSD) is in the respirable range (≤ 5 micron)

Methods for Inhaled Drug Delivery

Metered Dose Inhaler (MDI)

- Propellant-driven aerosolization
- Fast aerosol delivery
- Non-aqueous formulation within canister
- Active pharmaceutical ingredient (API) can be suspended or in solution
- Deposits typically as dry particles but may be dependent on formulation

Dry Powder Inhaler (DPI)

- Patient inhalation-driven aerosolization
- Blister/capsule/reservoir presentations
- Solid blend of API and carrier (e.g., lactose) particles/agglomerates
- Deposits as dry particles of drug and/or agglomerates

Inhalation Solution/Suspension for Nebulization

- Nebulizer-driven aerosolization
- Aqueous formulation within ampules
- API can be suspended or in solution
- Deposits as droplets containing dissolved or suspended drug

Inhalation Spray

- Device-driven aerosolization
- Slower aerosol delivered over a longer duration
- Aqueous formulation within cartridge
- API in solution
- Deposits as droplets containing dissolved drug

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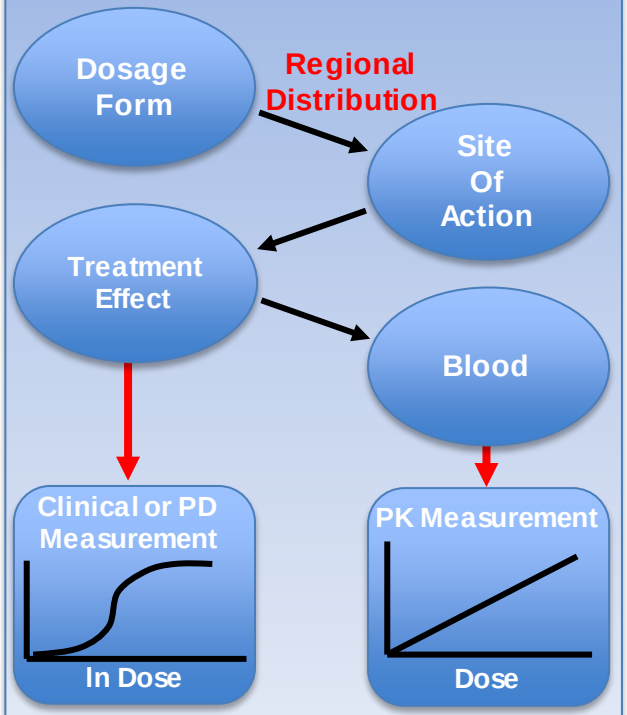
https://www.kitabis.com/img/15e6f7b119ecd53617e7f8453d5fd7c7-nebAndDrug.jpg

http://www.fpanetwork.org/fv/groups/internet/documents/web_assets/advair-diskus.jpg
https://pro.boehringer-ingelheim.com/us/products/spiriva/copd/respimat-device

Sources of Complexity and Challenges with Locally Acting OIDPs

Patient Related



Device Related

- Drug-device combination products
- Designs vary significantly across dosage forms
- Patient-device interactions (e.g., user interface, inhalation effort)

Formulation Related

- Physicochemical properties
- Types and amounts of inactive ingredients

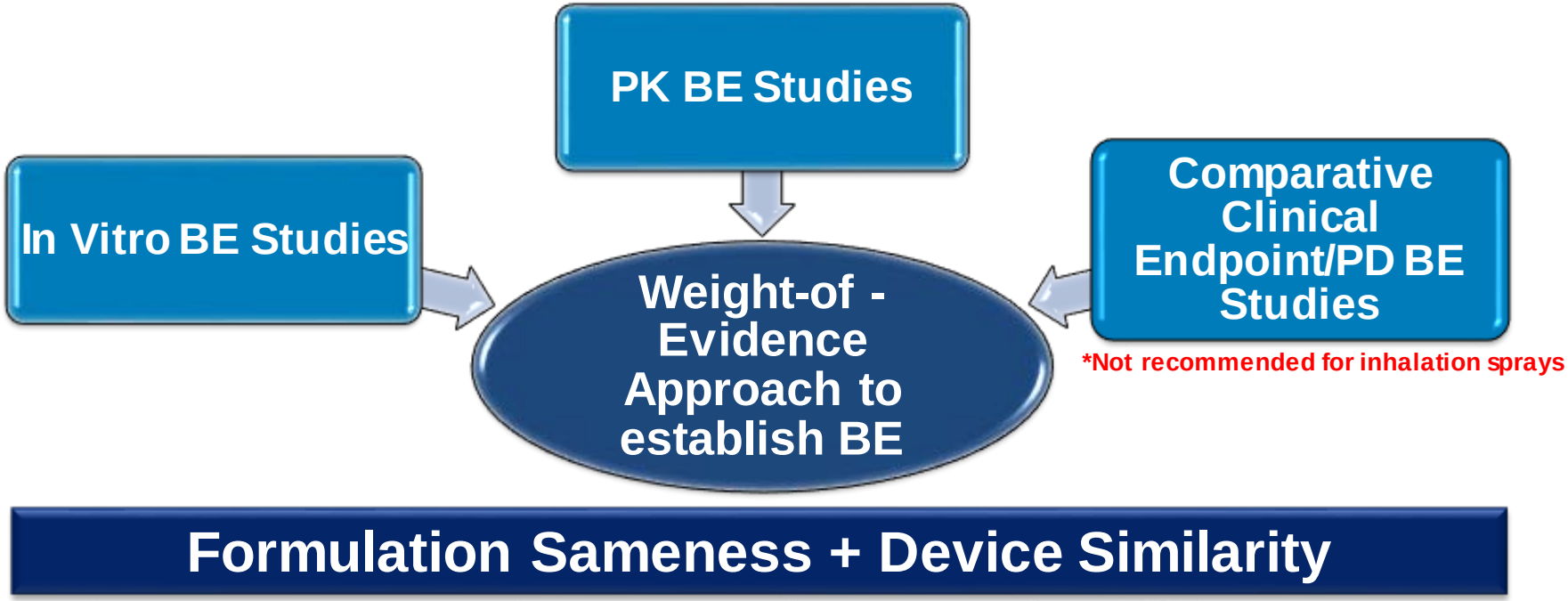
Administration Route	Site of Action	Drug State	Dosage Form
Inhalation	Local	Solution	Spray
		Suspension	Suspension
		Solution	Solution
		Solution	Aerosol, Metered
		Suspension	Aerosol, Metered
		Solid Blend	Powder
	Systemic	Solid Blend	Powder

Newman B, Witzmann K. Addressing the Regulatory and Scientific Challenges with Generic Orally Inhaled Drug Products. *Pharmaceut Med.* 2020 Apr;34(2):93-102. doi: 10.1007/s40290-020-00327-y. PMID: 32112304.

PK: pharmacokinetic
PD: pharmacodynamic
OIDP: orally inhaled drug product

Establishment of BE for OIDPs

- **To address challenges for locally-acting OIDPs → *Weight-of-Evidence Approach***
  - ***Locally-acting metered dose inhalers (MDIs), dry powder inhalers (DPIs), and inhalation sprays***



PK: pharmacokinetic
PD: pharmacodynamic

What about Inhalation Solutions and Suspensions for Nebulization?

Inhalation Solutions

- Consideration for biowaiver covered under 21 CFR 320.22(b)(3)
  - **Recommends formulation Qualitative (Q1) / Quantitative (Q2) sameness with the reference listed drug (RLD)**
- Non-Q1/Q2 formulations, additional characterization studies may be needed to show that any differences do not impact absorption of the active ingredient or its systemic / local availability for locally acting products

Contains Nonbinding Recommendations

Draft Guidance on Revefenacin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Revefenacin

Dosage Form; Route: Solution; inhalation

Strength: 175 mcg/3 mL

Waiver

A. To qualify for a waiver of evidence of in vivo bioavailability (BA) or bioequivalence (BE) study requirement under 21 CFR 320.22(b)(3), generic versions of revefenacin (175 mcg/3 mL) inhalation solution should contain the same active drug ingredient in the same concentration and dosage form as the Reference Listed Drug (RLD) product and contain no inactive ingredient or other change in formulation from the RLD that may significantly affect systemic or local availability.

B. For an inhalation solution drug product for nebulization that differs from the RLD in inactive ingredients [as permitted by the chemistry, manufacturing and controls regulations for Abbreviated New Drug Applications (ANDAs), 21 CFR 314.94(a)(9)(v)], the regulation specifies that the prospective applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

Additional Comments:

In general, evidence to demonstrate that the formulation of the test product should not alter the systemic or local availability of revefenacin, compared to that of the RLD product, may be based upon a comparison of the formulation composition as well as relevant quality and performance attributes of the test and RLD products.

If the test and RLD products are not qualitatively (Q1) and quantitatively (Q2) the same as defined in the guidance for industry, *ANDA Submissions – Refuse-to-Receive Standards* (December 2016, Revision 2), relevant quality and performance attributes should include appearance, pH, osmolality and any other potentially relevant physical and chemical properties, characterized for a minimum of three batches of the test and three batches (as available) of the RLD product.

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_210598.pdf

Inhalation Suspensions

- Recommendations may vary depending for **API** and **formulation complexity**
- For budesonide inhalation suspension:
  - Test formulation should be Q1/Q2 the same as the RLD
  - Demonstrating BE can be done using either:
    - **In vitro BE studies**
    - **In vitro + in vivo BE studies**
  - BE studies should be conducted for all strengths
  - Recommended BE studies for lower strengths dependent on properties of the micronized API used between high and low strengths

Contains Nonbinding Recommendations

Draft Guidance on Budesonide

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Budesonide

Form/Route: Suspension/Inhalation

Recommended studies:

1. **Testing Requirements for the Highest Strength (1 mg/2 mL) Product:**

The generic budesonide suspension/inhalation product must be qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug product (RLD).

Option A. In Vitro Bioequivalence Studies Alone:

The following in vitro comparative tests are recommended. Pari LC Plus Nebulizer/Pari Master compressor system is recommended for those tests requiring nebulization. The tests include:

1) Sameness of polymorphic form of the drug substance based on X-ray diffraction.

2) Sameness of shape (crystalline habit) of the drug substance.

3) Comparative Unit Dose Content (UDC) of drug in the ampules.

4) Comparative Mean Nebulization Time (MNT) and Mean Delivered Dose (MDD): The test should be conducted at the mouthpiece (% nominal dose) at the labeled flow rate of 5.5 L/min through such time that mist is no longer coming out of the mouthpiece.

5) Comparative drug particle and agglomerate Particle Size Distribution (PSD) in the suspension (in the ampoule): The PSD determination should be based on a validated method. Validation should demonstrate method sensitivity to drug particle size over the expected size range in the suspension.

6) Comparative drug particle and agglomerate PSD in the nebulized aerosol: Recommended method for this test is the aerodynamic particle size distribution (APSD) of the nebulized aerosol based on Apparatus 5 (USP <601>) at a flow rate of 15 L/min through the Apparatus. We recommend the study be conducted based on USP <1601> using the Pari LC Plus Nebulizer/Pari Master compressor system. The amount of drug deposited on the induction port, the seven stages of the cascade impactor, and the sum of the back-up filter and micro-orifice collector (MOC) should be submitted.

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Budesonide_Inhalation_Sus_20929_RC_09-12.pdf

Recommended In Vitro BE Studies

- Better sensitivity, lower variability, and easier to control than comparative clinical endpoint BE studies
- Conducted with all strengths, at least 3 batches of test (T) and reference (R) products, with no fewer than 10 units from each batch
- SAC and APSD are believed to affect the total and regional deposition of drugs in the lung
- SAC and APSD dependent on, and sensitive to, product- and process-related factors (e.g., API/Carrier physicochemical properties, device properties, process conditions)
- For inhalation sprays, spray duration and velocity are recommended since the aerosol is slowly released over a longer duration (may affect product use/performance)

DPIs

- **SAC**
  - Beginning (B), middle (M) and end (E) lifestages
  - 3 flow rates
- **APSD**
  - B and E lifestages
  - 3 flow rates

MDIs

- **SAC**
  - B, M and E lifestages
- **APSD**
  - B and E lifestages
- **Spray Pattern**
  - B lifestage
  - 2 distances from actuator mouthpiece
- **Plume Geometry**
  - B lifestage
- **Priming / Repriming**
  - (if required by the R product)

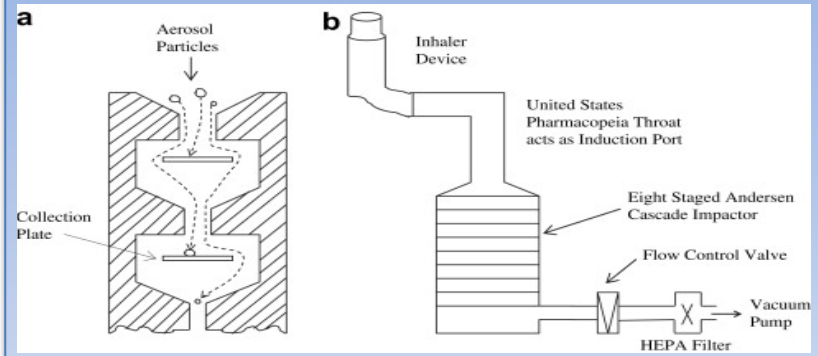
Inhalation Sprays

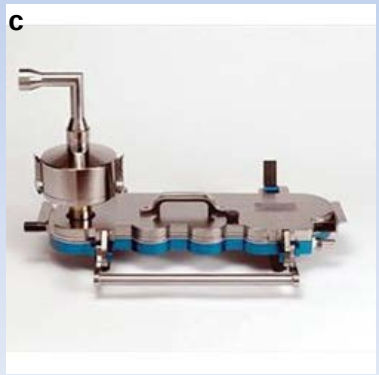
- **SAC**
  - B, M and E lifestages
- **APSD**
  - B and E lifestages
  - Minimize water evaporation via humidity or cooling
- **Spray Pattern**
  - B lifestage
  - 2 distances from nozzle
- **Plume Geometry**
  - B lifestage
- **Priming / Repriming**
  - (if required by the R product)
- **Spray Duration**
  - B and E lifestages
- **Spray Velocity**
  - B and E lifestages
  - BE on plume front velocity at 1 distance 8-12 cm from nozzle

SAC: Single Actuation Content
APSD: Aerodynamic Particle Size Distribution
API: Active Pharmaceutical Ingredient

Aerodynamic Particle Size Distribution (APSD) Characterization

Cascade Impaction Methods





(a) Schematics of Andersen Cascade Impactor (ACI) working principle

(b) ACI experimental setup

(c) Next Generation Impactor (NGI) cascade impactor with USP Induction Port

(d) Fast Screening Impactor (FSI) *(left)* and Fast Screening Andersen (FSA) *(right)* cascade impactors with USP Induction Port

- Study design considerations related to dosage form tested
  - DPI – varied flow rates
  - Inhalation Spray – humidity/cooling
- Population bioequivalence (PBE) based on impactor sized mass (ISM)
  - Total mass of all impactor stages except the top stage added to filter mass
- Also measured
  - Mass median aerodynamic diameter (MMAD)
    - Aerodynamic diameter is particle diameter multiplied by square root of particle density divided by water density
  - Geometric standard deviation (GSD)
  - Fine particle mass (FPM)
    - Mass of particles with diameter <5 µm

Kulkarni VS. Handbook of non-invasive drug delivery systems: science and technology. Elsevier; 2009.
https://www.selectscience.net/images/products/2370_Pic-11_288_0_0_0_362_299.jpg
https://tsi.com/getmedia/6ad8ea8a-41db-4de5-ba0b-a6136b3dfb93/MSP-Pharma-AIM-Method?width=400&height=300&ext=.jpg

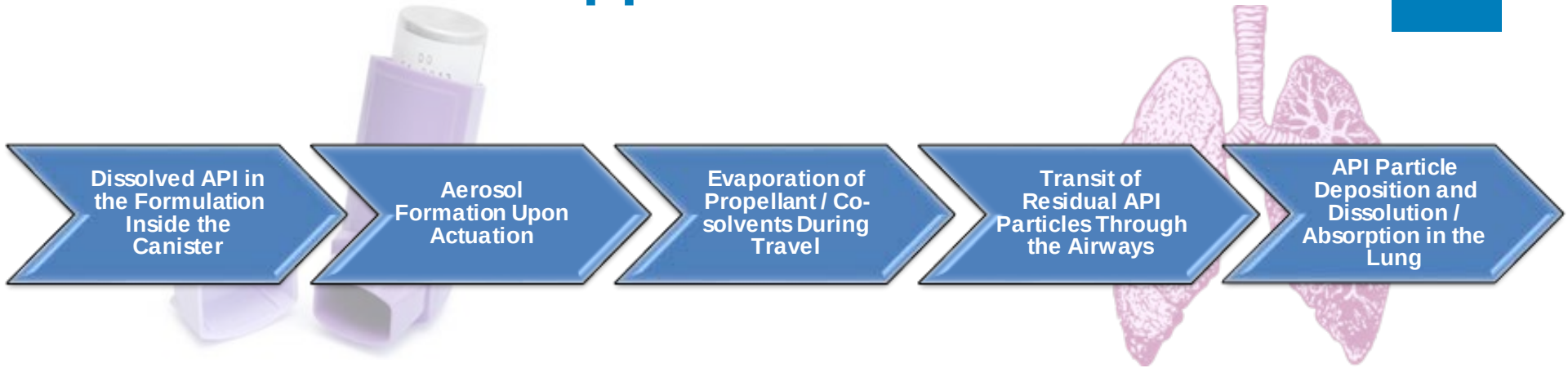
Recommended In Vivo Pharmacokinetic BE Studies

In Vivo BE Parameter	DPIs	MDIs	Inhalation Sprays
Study Design	Fasting, single-dose, two-way crossover, comparative PK study		
Objective	Determine differences in systemic exposure between drug products		
Strengths	All strengths should be tested since the relationship between PK dose proportionality across multiple strengths, in vitro performance parameters, and product characteristics are not well understood		
Dose	A minimum number of inhalations sufficient for PK characterization using a sensitive analytical method		
Study Population	Adult males and non-pregnant females, general population		
BE Endpoints and Criteria	The 90% confidence interval for the geometric mean T/R ratios for AUC and Cmax should fall within the limits of 80 – 125%		

Recommended In Vivo Comparative Clinical Endpoint / Pharmacodynamic BE Studies

In Vivo BE Parameter	DPIs	MDIs	Inhalation Sprays
Study Design	• Randomized, placebo-controlled, parallel or crossover comparative clinical endpoint (CEP) or pharmacodynamic (PD) BE study • Comparative CEP should contain a placebo run-in period followed by the treatment period of placebo, T, and R • Study sensitivity: Comparative CEP (effect over placebo), PD study (adequate dose-response)		Not applicable
Objective	Determine differences in local delivery at the site of action between drug products		Not applicable
Strengths	Lowest labeled dose (comparative CEP study)		Not applicable
Dose	Single or multiple-dose (based on mechanism of action)		Not applicable
Study Population	One patient population indicated in the approved labeling		Not applicable
BE Endpoints and Criteria	• The 90% confidence interval for geometric mean T/R ratios for the endpoint(s) should fall within the limits of 80 – 125% (comparative CEP study) • Using dose-scale analysis, the 90% confidence interval for relative bioavailability (F) should fall within 67.00-150.00% (PD Study)		Not applicable

Alternative BE Approaches: Solution MDIs



- Local delivery of the API to the site of action is a complex, multi-step process with each step impacting the next
- The comparative CEP BE study incorporates all steps from actuation to deposition, including those shown above, when evaluating whether a T and R OIDP have equivalent local drug delivery
- Similarly, an alternative approach to the comparative CEP BE study is recommended to contain in vitro, in silico, and/or alternative in vivo studies (e.g., PK BE study) to account for the different steps/factors impacting local delivery of the API to the site of action
- Like the weight-of-evidence approach for OINDPs, the selected studies in the alternative BE approach are recommended to **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***

https://www.dreamstime.com/stock-photos-asthma-inhaler-image24790423

OIDP: Orally Inhaled Drug Product

Alternative BE Approaches: Solution MDIs

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

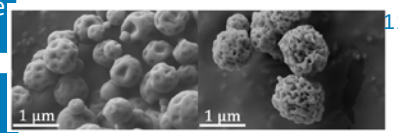
Characterization of Emitted Sprays (velocity profiles and evaporation rates)
- Understand droplet size and evaporation process of formulation emitted from the device

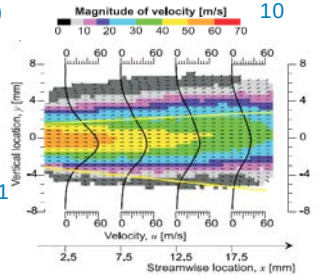
Morphology Imaging Comparisons (char. of full range of residual drug particle sizes)
- Understand residual particle morphology and size distribution of formulation emitted from the device

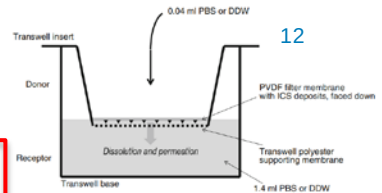
Dissolution
- Understanding how API dissolved at the site of action for absorption once deposited

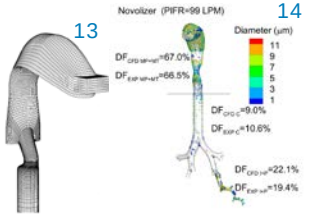
Quantitative Methods and Modeling (e.g., CFD, PBPK)
- In vitro-in vivo correlations (bridge gap between in vitro product performance and regional drug deposition)

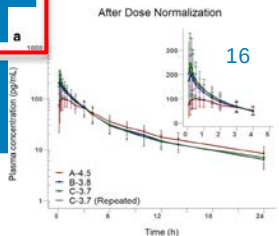
Alternative PK BE Studies
- Understanding how PK studies may correlate to local deposition

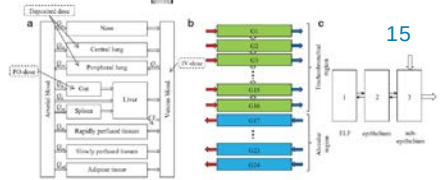












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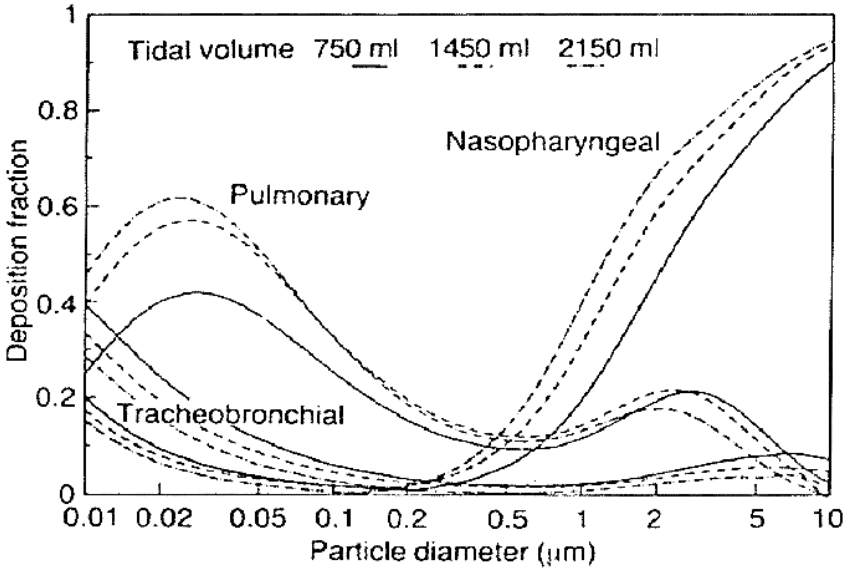
* Refer to the draft product-specific guidances for *Beclomethasone Dipropionate Inhalation Aerosol, Metered* (Rec Jan 2019; Rev Mar 2020), *Beclomethasone Dipropionate Inhalation Aerosol, Metered* (Rec Jan 2016; Rev Mar 2020), *Ipratropium Bromide Inhalation Aerosol, Metered* (Rec Mar 2015; Rev Mar 20201), *Cidesonide Inhalation Aerosol, Metered* (Rec Jan 2016; Rev Mar 2021)

Alternative Semi-Empirical Regional Deposition Modeling

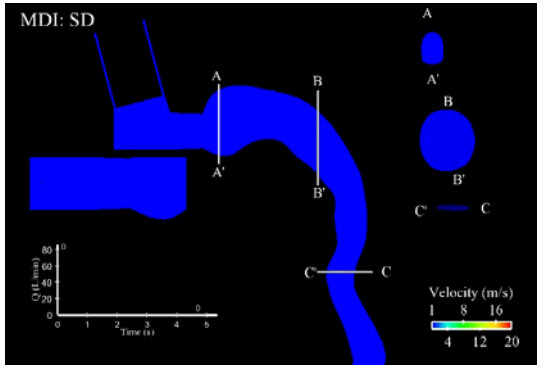


Deposition fraction predictions in nasopharyngeal, tracheobronchial, and pulmonary regions according to National Council on Radiation Protection and Measurements (NCRP) model (Figure from Phalen et al.[17])

- Algebraic, semi-empirical models
- Developed for toxicology
- Branch-specific deposition probability
- Deposition summed across branch levels to obtain regional deposition

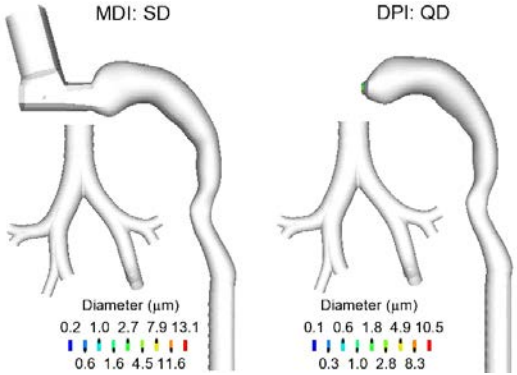
Computational Fluid Dynamics (CFD) Modeling

- Prediction of fluid and particle transport
- Allows for consideration of realistic geometries
- Validated with in vitro or in vivo data



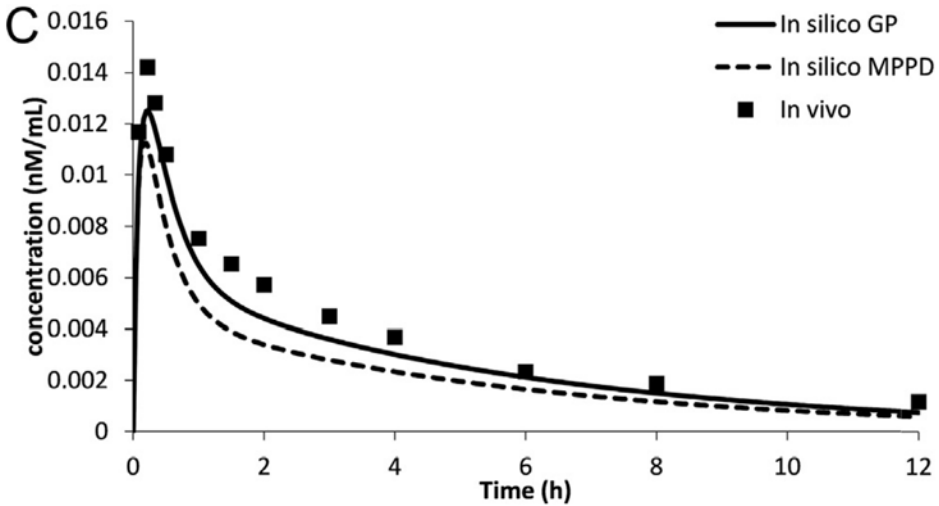
Metered Dose Inhaler (MDI)

Simulations from Longest et al.[18]



Dry Powder Inhaler (DPI)

Physiologically Based Pharmacokinetic (PBPK) Modeling



Plasma concentration of albuterol sulfate following administration of a Metered Dose Inhaler (MDI) formulation, where GastroPlus (GP) and Multiple Path Particle Dosimetry (MPPD) software packages were used to estimate drug deposition (Figure from Wu et al.[19] with in vivo data from Du et al.[20])

- Compartmental model
- Prediction of local and systemic PK
  - Dissolution in mucus layer
  - Absorption through lung tissue
  - Metabolism in lung tissue
  - Integration with systemic model
- Validated with in vivo PK data

Conclusions

- Respiratory system diseases impact a wide range of physiological systems in the lungs and pose a significant health and economic burden on patients.
- OIDPs are complex drug-device combination products that can pose challenges for generic development.
- Establishing BE with locally-acting OIDPs uses the weight-of-evidence approach, which generally includes a combination of in vitro and in vivo methods, along with formulation sameness and device similarity.
- To address the challenges with CCEP or PD BE studies, FDA has provided recommendations on alternative approaches for establishing BE for locally-acting solution-based MDIs.
- As part of these alternative BE approach recommendations, in silico methods may provide a way to better understand the relationship between regional lung deposition and regional absorption, as well as between results from in vitro and in vivo BE studies.

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