U.S. FOOD & DRUG ADMINISTRATION

Bioequivalence Approaches for Orally Inhaled Drug Products

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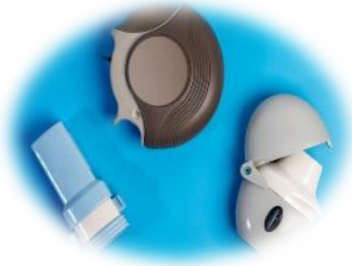
April 15, 2024



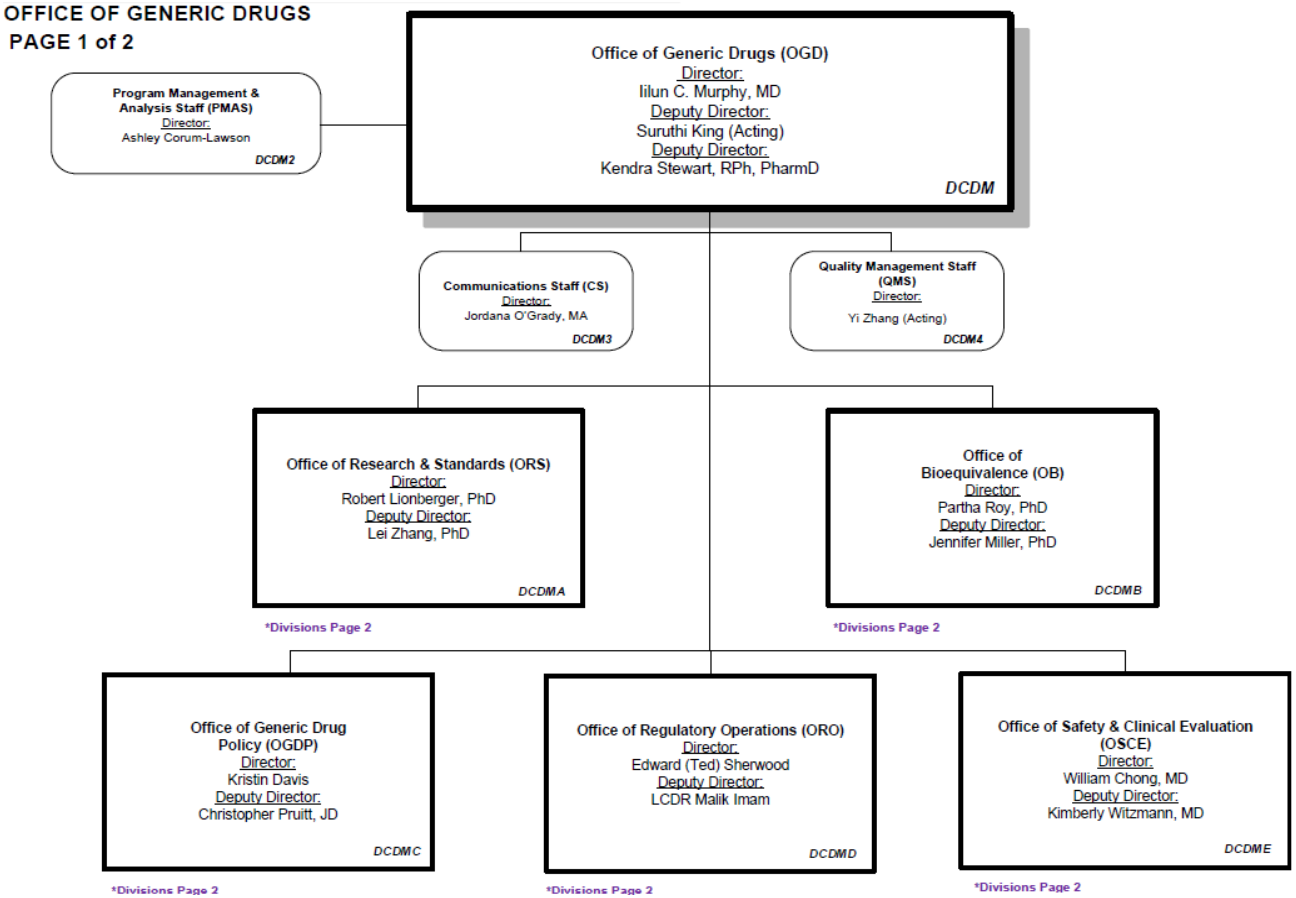
Outline

- Background on bioequivalence (BE) approaches for orally inhaled drug products (OIDPs)
- Current use of alternative BE approaches to the comparative clinical endpoint (CCEP) BE study for OIDPs
- Discussion on OIDP generic approvals

Bioequivalence (BE) Approaches

Orally Inhaled Drug Products (OIDPs)

Office of Generic Drug (OGD) Organization Chart



OGD Organization Chart Cont'd.

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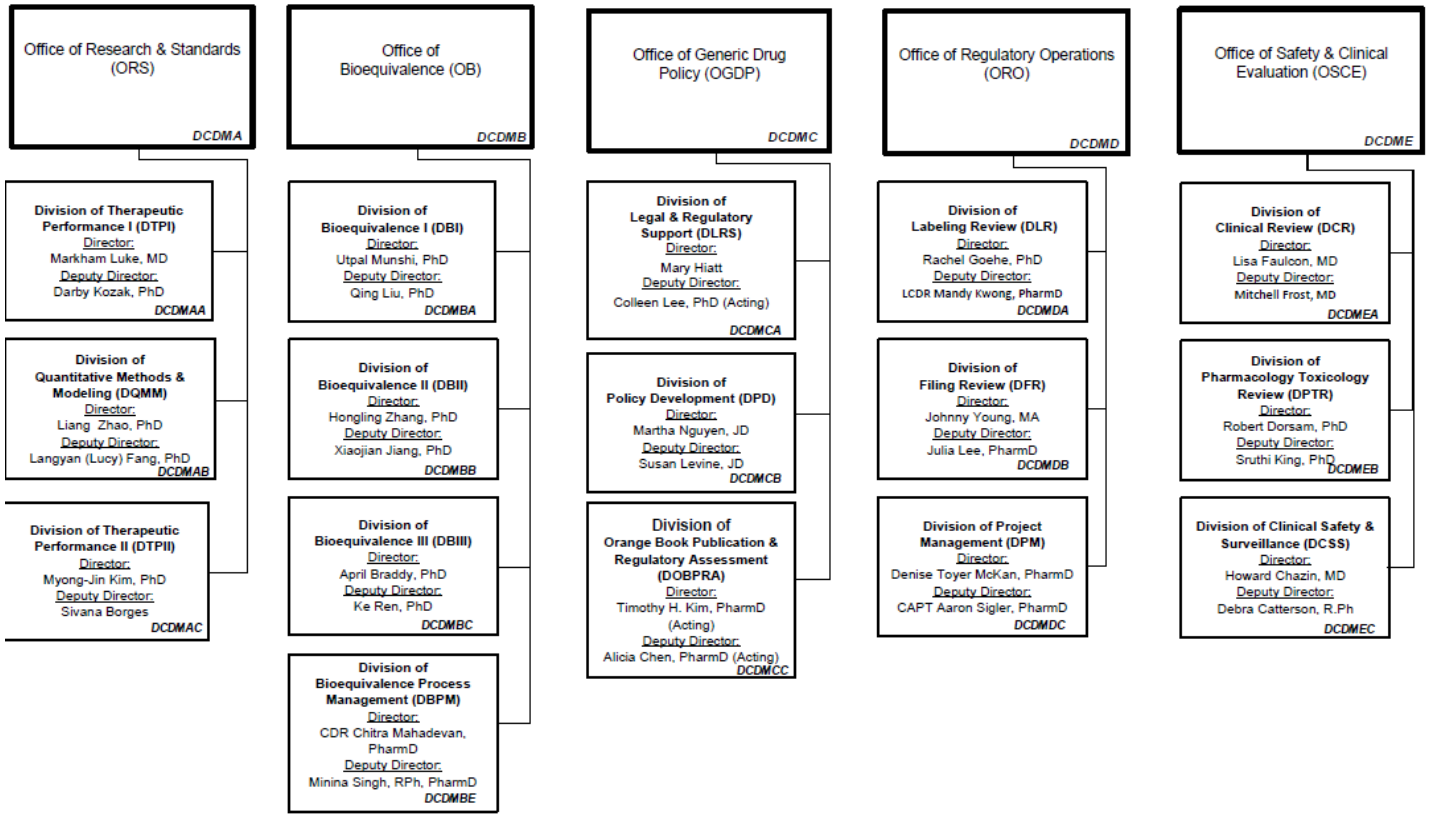


Methods for Inhaled Drug Delivery

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

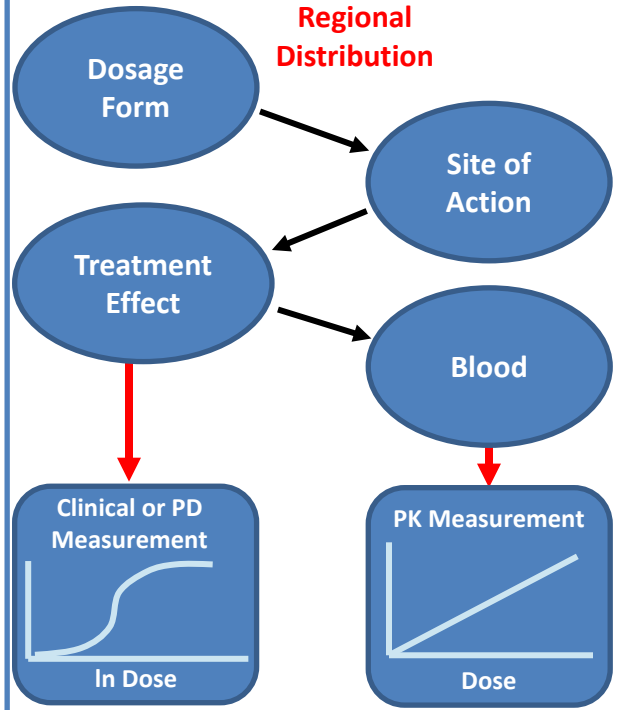
- Device-driven aerosolization
- Slower aerosol delivered over a longer duration
- Aqueous formulation within cartridge
- API in solution
- Deposits as droplets containing dissolved drug

https://www.pikpng.com/downpngs/hiRwxbo_asthma-attackers-swim-class-asthma-inhalers-clipart/
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 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

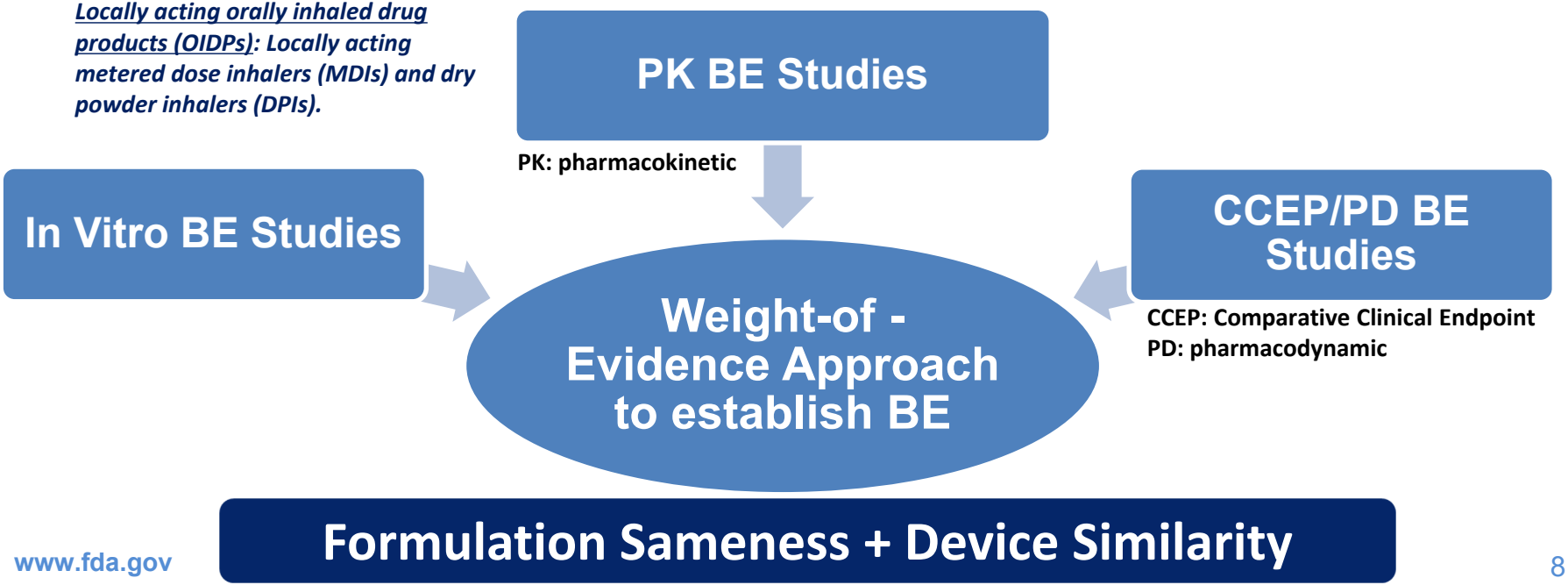
PK: pharmacokinetic
PD: pharmacodynamic OIDP: orally inhaled drug product

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.

FDA's Historical Approach for Establishment of Bioequivalence (BE) for OIDPs

- **Locally Acting BE Establishment**: ***Absence of significant difference*** in which the drug becomes available at the ***site of action (i.e., lungs).***
- **To address challenges for locally acting OIDPs → *Weight-of-Evidence Approach.***

***Locally acting orally inhaled drug products (OIDPs)*: Locally acting metered dose inhalers (MDIs) and dry powder inhalers (DPIs).**



Inhalation Spray Products

- Guidance for Industry, *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products-Chemistry, Manufacturing, and Controls Documentation* (July 2002) defines inhalation sprays as follows:

  *"An inhalation spray drug product consists of the formulation and the container closure system. The formulations are **typically aqueous based** and, by definition, **do not contain any propellant**. Aqueous-based oral inhalation sprays must be sterile (21 CFR 200.51). Inhalation sprays are **intended for delivery to the lungs by oral inhalation for local and/or systemic effects**. The products contain therapeutically active ingredients and can also contain additional excipients. The formulation can be in unit-dose or multidose presentations... The dose is delivered by the integral pump components of the container closure system to the lungs by oral inhalation for local and/or systemic effects."*

FDA draft guidance for industry, *"Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products-Chemistry, Manufacturing, and Controls Documentation" (July 2002)*

Inhalation Spray Products

- Currently, there are four inhalation spray drug products approved on the market

Product name	Active Pharmaceutical Ingredient (API)
COMBIVENT RESPIMAT	albuterol sulfate; ipratropium bromide
STRIVERDI RESPIMAT	olodaterol hydrochloride
SPIRIVA RESPIMAT	tiotropium bromide
STIOLTO RESPIMAT	olodaterol hydrochloride; tiotropium bromide

- According to their approved labeling, these four inhalation spray products utilize the RESPIMAT® Soft Mist™ Inhaler device to produce a ***metered, slow moving aerosol cloud*** following actuation.

Challenges in Establishing BE

- Inhalation sprays exhibit many similar features to ***aqueous-based solutions for nebulization***, ***aqueous-based solution nasal sprays*** and ***propellant-based solution MDIs***.
- The spray from inhalation spray products that are currently marketed have the following characteristics:
  - **Aqueous drug solution droplets** (resembling nebulized aerosol)
  - **Longer duration** (e.g., 1.5 seconds; approximately 10 times that of an MDI)
  - **Slow moving** (velocity approximately 1/10th of that of an MDI)
- These characteristics may impact how the inhalation spray is ***used***, as well as its ***performance***.
- Development of BE recommendations for inhalation spray products has been supported by **Generic Drug User Fee Amendments (GDUFA)-funded research**.

Dalby RN et al. International Journal of Pharmaceutics. 2004; 283: 1–9.
Dalby RN. et al. Medical Devices: Evidence and Research. 2011; 4: 145-155.

BE Approach for Inhalation Spray Products

Formulation Sameness (Q1 and Q2)* + Device Similarity

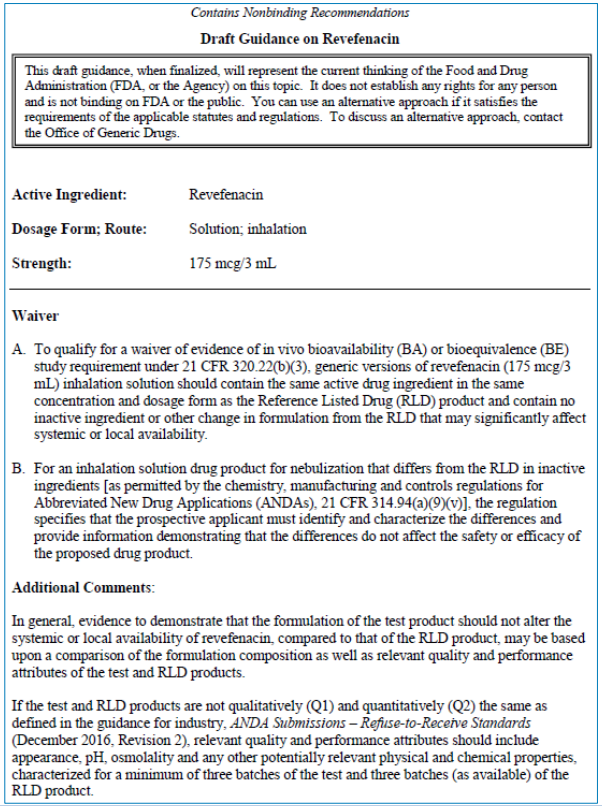
*Does **not** recommend a comparative clinical pharmacodynamic BE study*

*Q1: Qualitative sameness; Q2: Quantitative sameness

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:

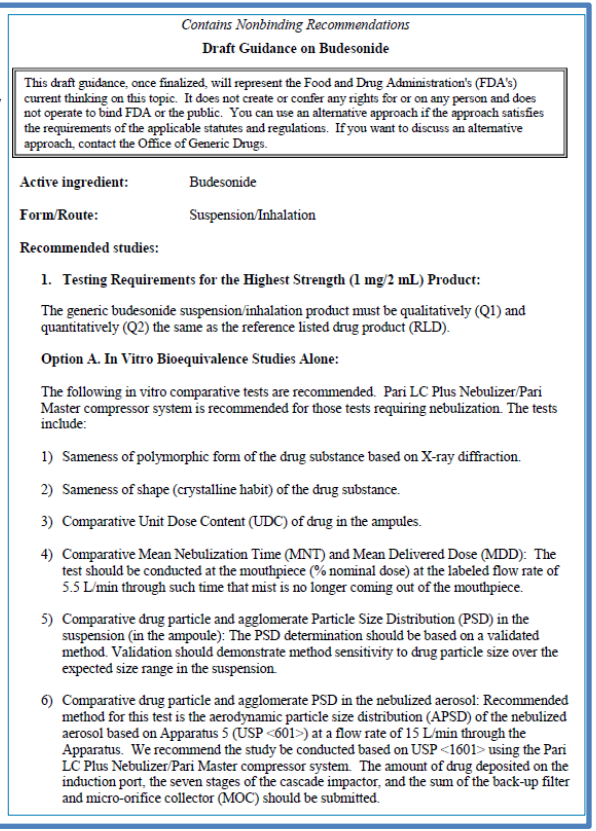
In general, evidence to demonstrate that the formulation of the test product should not alter the systemic or local availability of revefenacin, compared to that of the RLD product, may be based upon a comparison of the formulation composition as well as relevant quality and performance attributes of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

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	Healthy males and non-pregnant females		
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

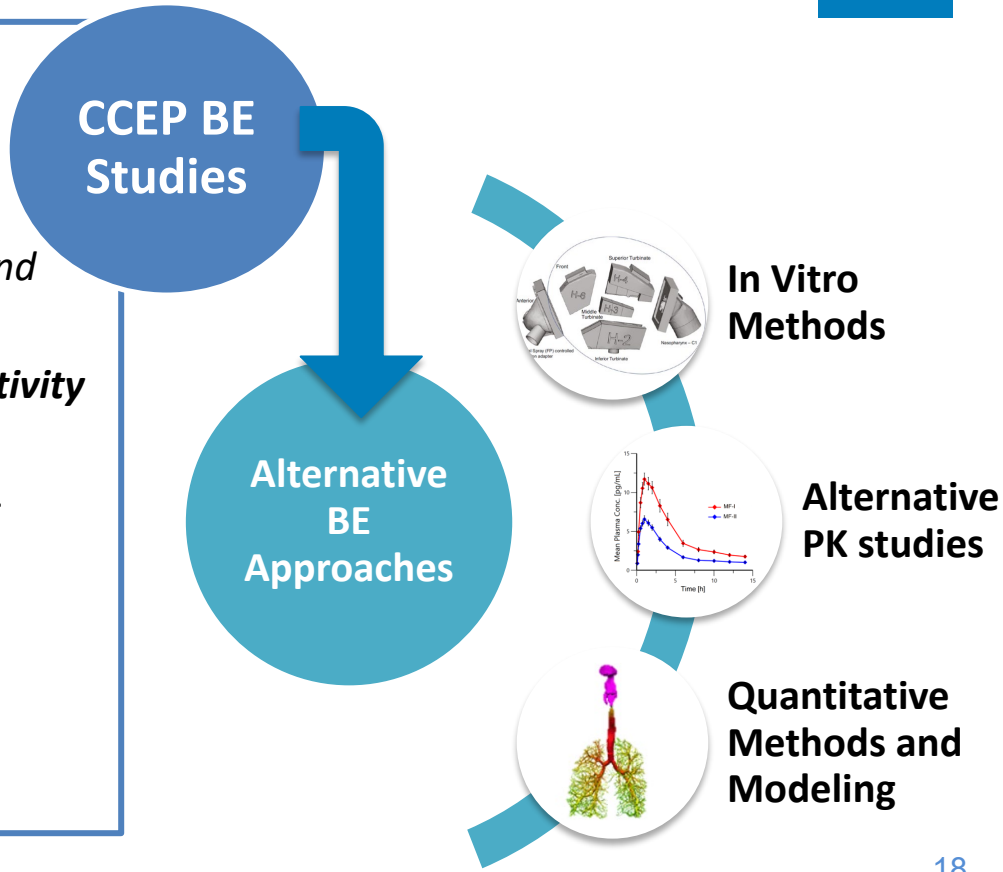
In Vivo BE Parameter	DPIs	MDIs	Inhalation Sprays
Study Design	• Randomized, placebo-controlled, parallel or crossover comparative clinical endpoint (CCEP) or pharmacodynamic (PD) BE study • CCEP BE study should contain a placebo run-in period followed by the treatment period of placebo, T, and RS • Study sensitivity: CCEP (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	Generally, the lowest labeled dose (CCEP BE 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 Approaches to the CCEP BE Study

Orally Inhaled Drug Products (OIDPs)

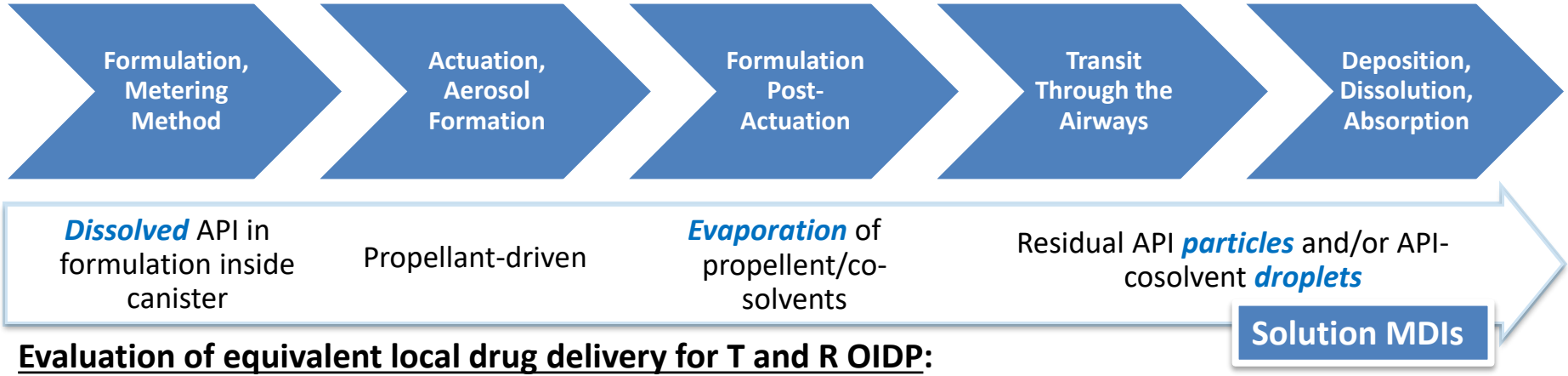
The Challenges with CCEP BE Studies

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



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



Evaluation of equivalent local drug delivery for T and R OIDP:

- The **CCEP BE study** incorporates ***all steps*** from actuation to deposition
- Similarly, **an alternative approach** to the CCEP 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 API delivery
  - Should ***work together*** to provide a ***comprehensive evaluation of the local drug delivery***
  - **In silico approaches** may be useful for demonstrating how results from different alternative BE studies work together
  - The ***types*** of alternative BE studies to include may depend on the specific OIDP dosage form and formulation

CCEP: Comparative Clinical Endpoint; OIDP: Orally Inhaled Drug Product

Alternative BE Approach: Solution MDIs

Product-specific guidances (PSGs) on *Beclomethasone Dipropionate Metered Inhalation Aerosol* (NDA 020911; NDA 207921), *Ipratropium Bromide Metered Inhalation Aerosol* (NDA 021757), and *Ciclesonide Metered Inhalation Aerosol* (NDA 021658)

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

Actuation, Aerosol formation

Characterization of Emitted Sprays (velocity profiles and evaporation rates)
- Understand emitted droplet size and evaporation process of formulation (volatiles + non-volatiles)

Formulation Post-actuation

Morphology Imaging Comparisons (characterization of full range of residual drug particle sizes)
- Understand residual particle morphology and size distribution of emitted formulation

Transit through the airways; Deposition, Dissolution, Absorption

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

APSD: Aerodynamic Particle Size Distribution

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

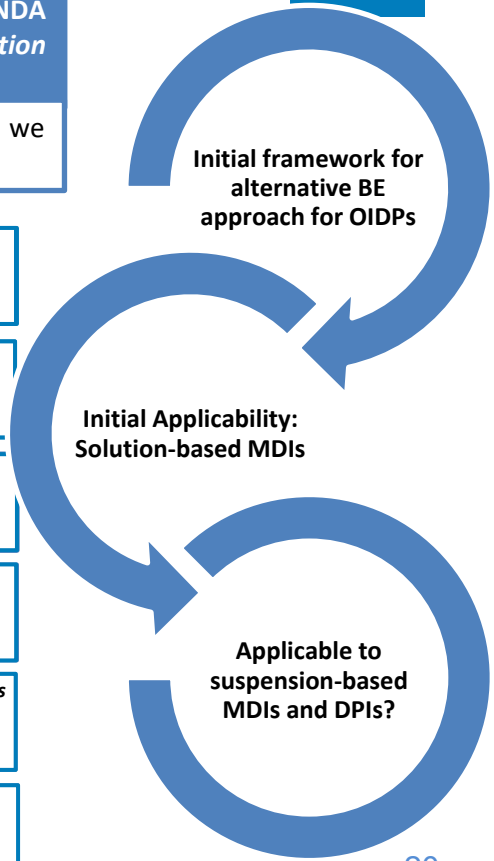
Methods for further support

Quantitative Methods and Modeling (e.g., PBPK, CFD studies)
- IVIVCs to bridge gap between in vitro product performance and regional drug deposition

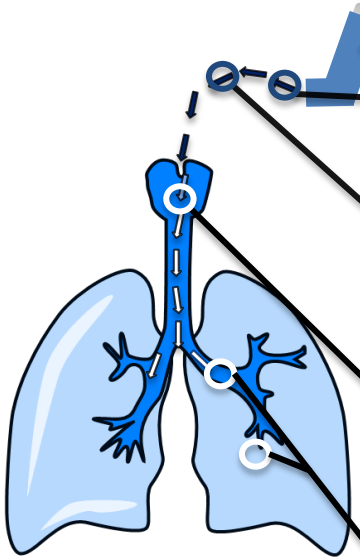
PBPK: Physiologically-based Pharmacokinetics
CFD: Computational Fluid Dynamics

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

PK: Pharmacokinetics



Potential Methods for Assessing Contributing Factors to Local Drug Delivery



Step 1
Formulation/Device Characteristics

Step 2
Actuation and Aerosolization

Step 3
Formulation Post-Actuation

Step 4
Airway Transit

Step 5
Deposition, Dissolution, Absorption

IN VITRO STUDY METHODS

- Realistic Aerodynamic Particle Size Distribution
- Dissolution
- Optical Suspension Characterization
- Droplet Size Distribution by Laser Diffraction
- Morphology-assisted Raman Spectroscopy (MDRS)
- Scanning Electron Microscopy (SEM)
- X-ray Tomography
- Shadowgraphic imaging/shadow motion analysis
- Phase Doppler Interferometry/Anemometry
- Particle Imagine Velocimetry
- Optical Photothermal Infrared Microscopy
- Atomic Force Microscopy – Infrared Microscopy
- Cell Permeability Assays

IN VIVO STUDY METHODS

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

IN SILICO STUDY METHODS

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

External Input Informs FDA Thinking on Alternative BE Approaches for OIDPs

Trainings Link: https://www.complexgenerics.org/education-training/
Event Materials: Link.

CENTER FOR RESEARCH ON COMPLEX GENERICS

FDA U.S. FOOD & DRUG ADMINISTRATION

- **Two-day workshop** to discuss the Agency's ***scientific understanding and regulatory perspective on alternative BE approaches*** with industry representatives and academic experts.
- In person attendees participated in small group discussions that provided FDA with valuable insight into the ***industry's experiences*** with alternative BE approaches and their thinking on potential approaches for complex OIDPs (suspension MDIs and DPIs).




External Input Informs FDA Thinking on Alternative BE Approaches for OIDPs

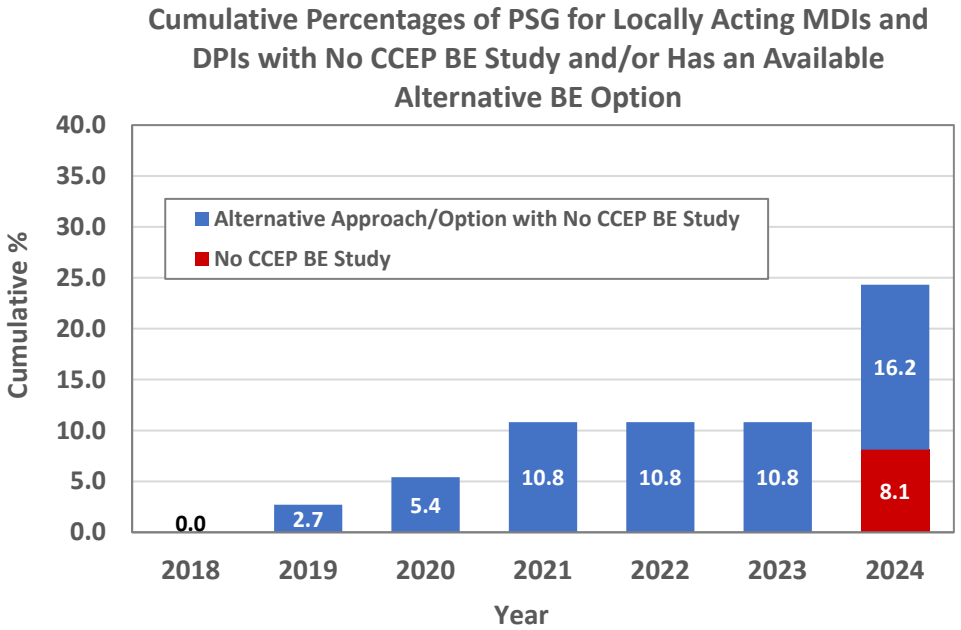
- Most **alternative approaches** are generally ***applicable to both MDIs and DPIs*** irrespective of their formulation.
- Certain approaches are ***more critical and informative.***
- Inclusion of a particular study may be ***product-specific*** (e.g., dependent on the drug substance properties).
- Some approaches useful for ***product development*** vs. others for assessing **BE.**

Useful Study Methods	• Realistic APSD • Dissolution • In silico methods
Potentially Useful or Confirmatory	• Particle morphology • Charcoal-block PK study
Study Methods with Limited Utility	• Evaporation rate and velocity profile evaluation • Pre-actuation characterization of the formulation

PSGs of Locally Acting MDIs and DPIs with No Recommended CCEP BE Study or Alternative BE Option Available

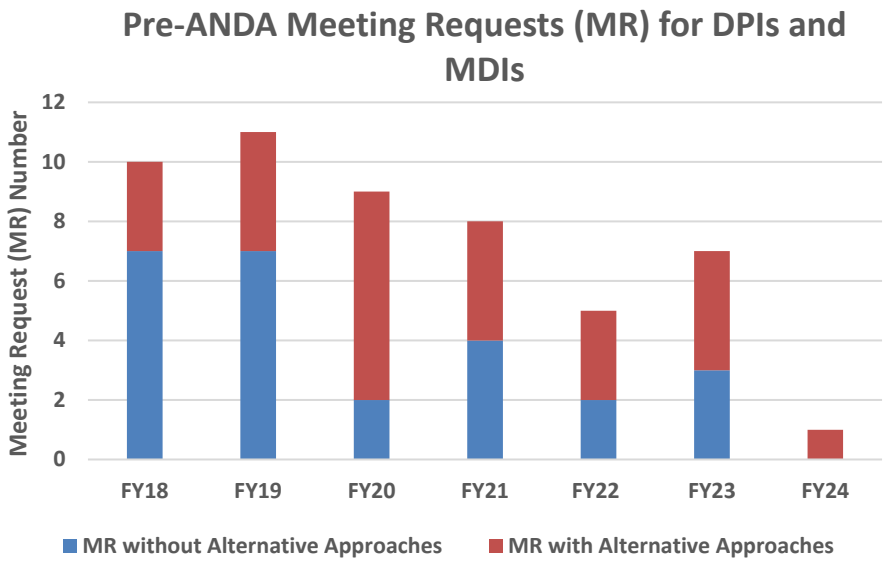
- Since 2018, FDA has **increased the percentage of available PSGs** for locally acting MDIs and DPIs
  - Recommend ***alternative approaches*** to CCEP BE studies
  - ***Do not recommend*** the CCEP BE study

- **2018**:
  - **0 %** of available PSGs had alternative BE approaches to a CCEP BE study (i.e., a CCEP BE study recommended in every case)
- **2019**:
  - **First alternative BE approach/option** available
- **2024**:
  - **8.1%** - PSGs with no recommended CCEP BE study
  - **16.2%** - alternative approach/option available
  - Total → **24.3%**



Pre-ANDA Meeting Requests: Input on Alternative Approaches

- FDA's **pre-ANDA meeting program** for prospective ANDA applicants:
  - **Clarify regulatory expectations** early in product development
  - Assist in developing **more complete submissions**
  - Promote a **more efficient** and **effective** ANDA assessment process
  - **Reduce the number of assessment cycles** required to obtain ANDA
- **51** pre-ANDA meeting requests received since FY18:
  - **51%** included **alternative approaches** to the CCEP BE study



Refer to FDA's guidance on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* for more details (https://www.fda.gov/media/107626/download)

Generic Drug Approvals

Orally Inhaled Drug Products (OIDPs)

Approved Generic DPIs and MDIs

Drug Substance	Brand Name	Approved ANDA	Approval Date	Generic Company
Fluticasone Propionate; Salmeterol Xinafoate	Advair Diskus Inhalation Powder (NDA 021077)	208891	January 30, 2019	Mylan Pharmaceuticals, Inc.
		203433	December 17, 2020	Hikma Pharmaceuticals USA Inc.
		213948	December 13, 2021	Teva Pharmaceuticals USA Inc.
Tiotropium Bromide	Spiriva Inhalation Powder (NDA 021395)	211287	June 20, 2023	Lupin Inc.
Albuterol Sulfate	ProAir HFA Inhalation Aerosol, Metered (NDA 021457)	203760	February 24, 2020	Padagis US LLC
		209954	August 24, 2020	Lupin Inc.
	Proventil HFA Inhalation Aerosol, Metered (NDA 020503)	209959	April 8, 2020	Cipla Ltd.
		207085	June 1, 2021	Sandoz Inc.
Budesonide; Formoterol Fumarate Dihydrate	Symbicort Inhalation Aerosol, Metered (NDA 021929)	211699	March 15, 2022	Mylan Pharmaceuticals, Inc.

FDA BE Recommendations for MDI: weight-of-evidence approach

Equivalent In Vitro Performance

1. Single actuation contents (SAC)
2. Aerodynamic particle size distribution (APSD)
3. Spray pattern
4. Plume geometry
5. Priming and repriming (if required by the R product)

Equivalent Systemic Exposure

Pharmacokinetic (PK) study

Equivalent Local Delivery

Pharmacodynamic (PD) study
or
Comparative clinical endpoint study

Formulation and Device Design

FDA BE Recommendations for DPI: weight-of-evidence approach

Equivalent In Vitro Performance

1. Single actuation contents (SAC)
2. Aerodynamic particle size distribution (APSD)

Equivalent Systemic Exposure

Pharmacokinetic (PK) study

Equivalent Local Delivery

Pharmacodynamic (PD) study
or
Comparative clinical endpoint study

Formulation and Device Design

Formulation Similarity

- Recommends qualitatively (Q1)/quantitatively (Q2) the same
- If Q2 different
  - Explain the reason, and provide pharmaceutical development data, involving in vitro testing of multiple drug-to-excipient ratios that encompass combinations below and above the ratios used in the test product and reference listed drug (RLD)
  - Maximum Daily Intake of excipient used in the test product should not exceed that in FDA approved inhalation products
  - The Q2 difference has no impact on BE, through in vitro and in vivo BE studies

Device Similarity

- Similar size and shape, same basic operating principle, sample number of doses, dose counter, etc.
- Threshold analysis per Guidance for Industry – Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (Jan 2017)
  - Labeling comparison
  - Comparative task analysis
  - Physical comparison of delivery device constituent part
- If the outcome of threshold analysis is that differences in design is other than minor
  - May consider re-design of the user interface to minimize differences from the RLD
  - Potential need for additional information and/or data, such as data from comparative human factor studies

Equivalent In Vitro Performance

- Conducted for each strength
- Use at least 3 batches each of test product and reference standard, with no fewer than 10 units from each batch
- Method validation
  - Testing method validation
  - Analytical method validation for HPLC
- Pivotal studies (details on the next slide)

Equivalent In Vitro Performance (cont'd)

- Pivotal studies

MDIs

1. SAC
   - B, M, E lifestages
   - Population bioequivalence (PBE) of SAC
2. APSD
   - B, E lifestages
   - PBE of impactor-sized mass (ISM)
   - Supportive evidence: Cascade impactor profiles, median aerodynamic diameter (MMAD), geometric standard deviation (GSD), and find particle mass (FPM)
3. Spray pattern
   - B lifestage
   - 2 distances
   - Qualitative comparison of spray shape
   - PBE of ovality ratio and area, or ovality ratio and Dmax
4. Plume geometry
   - B lifestage
   - Point estimate for plume angle and width within 90%-111%
5. Priming and repriming (if required by the R product)
   - PBE of the emitted dose of a single actuation immediately following the specified number of priming or repriming actuations specified by RLD labeling

DPIs

1. SAC
   - B, M, E lifestages
   - 3 flow rates
   - PBE of SAC
2. APSD
   - B, E lifestages
   - 3 flow rates
   - PBE of ISM
   - Supportive evidence: Cascade impactor profiles, MMAD, GSD, and FPM

Equivalent Systemic Exposure

- Conducted for each strength
- Fasting PK study in healthy subjects
- Analytical method validated with adequate sensitivity
- The 90% confidence interval (CI) for the geometric mean T/R ratios for AUC and Cmax within 80.00 – 125.00%

Equivalent Local Delivery

- PD study or comparative clinical endpoint study conducted generally for the lowest strength in patients
- For PD study using dose-scale analysis, the 90% CI for relative bioavailability (F) within 67.00-150.00%
- For comparative clinical endpoint study, the 90% CI for geometric mean T/R ratios for the endpoint(s) within 80.00 – 125.00%

Study Design Recommendation

- Follow recommendations in the product-specific guidance
- Differences from product-specific guidance needs justifications, and the acceptability is evaluated on a case-by-case basis.
- May discuss in pre-ANDA communications

Differences from Product-Specific Guidance

- Uncommon in in vitro and PK studies
- May happen in PD/clinical endpoint studies
  - E.g., differences in study population such as age, percent of predicted forced expiratory volume in 1 second (FEV_1), percent reversibility of FEV_1 criteria for asthma patients

Bridging Studies

- When and why bridging studies may be needed
  - For in vitro, PK, PD, and comparative clinical endpoint BE studies, prefer to use test batches that represent the proposed to-be-marketed/ commercial product.
  - However, changes in the drug product (e.g., in device, formulation and manufacturing) may occur after BE studies are completed.
  - Depending on the specific change, bioequivalence between the post-change test product and the RLD may be established by
    - Repeating the complete set of recommended BE studies between the post-change test product and the reference standard
    - Conducting in vitro or in vivo bridging studies between the post-change test product and the reference standard

Bridging Studies (cont'd)

- The necessity and type of bridging studies depends on the specific changes.
- Case Study: an MDI product with incorporation of a dose counter
  - The applicant proposed to incorporate a dose counter after all of the BE studies were conducted using the test product without dose counter.
  - Recommended conducting, at minimum, in vitro BE studies (SAC, APSD, spray pattern, plume geometry, and priming and repriming) comparing the post-change test product with a dose counter to the reference standard with a dose counter.
  - Upon review of the bridging data with dose counter, additional studies may be requested.

Alternative BE Approaches in Lieu of the Comparative Clinical Endpoint Study

- Alternative approaches should be justified with comprehensive data and explanation.
  - E.g., Applicants are recommended to include the level of importance of each study to the overall alternative approach and discuss the limitations of each study in the submission.
- Applicants may discuss their alternative BE approaches with the Agency in pre-ANDA communications and in meetings after their ANDAs are submitted.

Conclusions

- **Respiratory 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.
- Traditionally, the **weight-of-evidence approach** is used for establishing BE of ***locally-acting OIDPs*** uses which generally includes a combination of in vitro and in vivo methods, along with formulation sameness and device similarity.

Conclusions

- 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***.
- More recent recommendations have continued the efforts by providing **PSGs for MDIs** and **DPIs** in which a ***CCEP BE study is not included*** or an ***alternative BE option is available***.
- Meetings with industry in the pre-ANDA setting have shown interest in **continuing discussions on alternative approaches** to CCEP BE studies for ***locally acting inhalation products***.

Conclusions

- Applicants are encouraged to follow recommendations in product-specific guidances.
- For BE studies, recommend to use test batches that represent the proposed to-be-marketed/ commercial product
  - If there are changes such as in device, formulation, and manufacturing, bridging studies may be needed.
- Differences from product-specific guidances and alternative approach in lieu of comparative clinical endpoint study can be discussed with the Agency.

Acknowledgements

- FDA/CDER/OGD/ORS
  - Sneha Dhapare
  - Liangfeng Han
  - Susan Boc
  - Anubhav Kaviratna
  - Md Abul Kaisar
  - Denise Conti
  - Elizabeth Bielski
  - Ross Walenga
  - Steven Chopski
  - Andrew Babiskin
  - Darby Kozak
  - Markham Luke
  - Liang Zhao
  - Lei Zhang
  - Robert Lionberger
- FDA/CDER/OGD/OB
  - Vipra Kundoor
  - Qing Liu
  - Ke Ren
  - Bing Li
- FDA/CDER/OPQ/OTR
  - Changning Guo
  - Sau Lee
- FDA/CDER/OPQ/ONDP
  - Renishkumar Delvadia
- FDA/CDER/OGD/OSCE
  - Kimberly Witzmann
- FDA/CDER/OTS/OCP
  - Bhawana Saluja
- External Research Collaborators
  - Günther Hochhaus
  - Jürgen Bulitta
  - Michael Hindle
  - Jagdeep Shur
  - Robert Price
  - Masahiro Sakagami
  - Peter Longest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