First Generic Drug Approval: Budesonide & Formoterol Fumarate Dihydrate Inhalation Aerosol (RLD: Symbicort): A Bioequivalence Perspective

SBIA 2023—Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session 5: Noteworthy Complex Generic Drug Approvals: Orally Inhaled Products

Zhen Xu, Ph.D.

Pharmacologist

Division of Bioequivalence III/Office of Bioequivalence/Office of Generic Drugs

CDER | U.S. FDA

September 14, 2023

Learning Objectives

- Describe FDA's bioequivalence approach for locally acting orally inhaled or nasal drug products (OINDPs)

- Able to summarize the bioequivalence (BE) studies recommended in the product-specific guidance (PSG) for generic version of Symbicort® metered dose inhalers (MDIs)

- Discuss a case study that uses alternative approach (e.g., sensitivity analysis) to support non-quantitative (Q2) formulation of a generic MDI product, compared to reference listed drug (RLD)

Representative OINDPs

	MDI	DPI	Soft Mist
β2-Agonists	ProAir® HFA (albuterol sulfate) Inhalation Aerosol Teva Specialty Pharmaceuticals	Serevent® Diskus® (salmeterol xinafoate) Inhalation Powder GlaxoSmithKline	Striverdi® Respimat® (olodaterol) Inhalation Spray Boehringer Ingelheim Pharmaceuticals, Inc.
Anticholinergics	Atrovent® HFA (ipratropium bromide HFA) Inhalation Aerosol Boehringer Ingelheim Pharmaceuticals, Inc.	Spiriva® Handihaler® (tiotropium bromide) Inhalation Powder Boehringer Ingelheim Pharmaceuticals, Inc.	Stiolto® Respimat® (tiotropium bromide and olodaterol) Inhalation Spray Boehringer Ingelheim Pharmaceuticals, Inc.
Corticosteroids	QVAR® (beclomethasone dipropionate) Inhalation Aerosol Teva Specialty Pharmaceuticals	Arnuity® Ellipta® (fluticasone furoate) Inhalation Powder GlaxoSmithKline	**Nasal Spray** Flonase® (fluticasone propionate) Nasal Spray GSK Consumer Healthcare
Combination β2-Agonists + Anticholinergics or Corticosteroids	Bevespi Aerosphere™ (glycopyrrolate and formoterol fumarate) Inhalation Aerosol AstraZeneca Pharmaceuticals	Breo® Ellipta® (fluticasone furoate and vilanterol) Inhalation Powder GlaxoSmithKline	**Nasal Aerosol** Qnasl™ (beclomethasone dipropionate) Nasal Aerosol HFA

Nebulizer

Pari LC Plus

Device Type:

Jet
Ultrasonic
Vibrating mesh

Formulation Type:

Solution vs.
Suspension

FDA's Weight of Evidence Approach for Locally Acting Metered Dose Inhalers

Equivalent In Vitro Performance

- Single Actuation Contents (SAC)
- Aerodynamic Particle Size Distribution (APSD)
- Spray Pattern
- Plume Geometry
- Priming and Re-priming

Equivalent Systemic Exposure

Based on In Vivo Pharmacokinetics (AUCs and Cmax) data

Equivalent Local Delivery

Based on Comparative Clinical Endpoint Study or Alternative Approach

Formulation and Device Sameness Between Test and Reference Products

- Valve, pump, and actuator designs should be as close as possible in all critical dimensions
- Metering chamber volumes and actuator orifice diameters should be the same
- Formulation: Qualitative (Q1) and quantitative (Q2) the same

Reference Listed Drug

Strengths: 80 µg/4.5 µg and 160 µg/4.5 µg /actuation

NDA 021929, AstraZeneca Pharmaceuticals, approved 07/21/2006

Indication: Treatment of asthma in patients 6 years of age and older. Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease

Online image: https://www.mmm-online.com/home/channel/pharmaceutical/symbicort-160-4-5/

PSG* for Budesonide and Formoterol Fumarate Dihydrate Metered Dose Inhaler

Formulation and Device	Qualitatively (Q1) and quantitatively (Q2) the same between Test and RLD; Similar device
In Vitro Studies	For both strengths: • SAC • APSD • Spray pattern • Plume geometry • Priming and repriming
In Vivo Pharmacokinetic BE Study	PK BE study on fasting condition, on both strengths
Comparative Clinical Endpoint Study	Lowest strength in asthma patients

**PSG link:*
https://www.accessdata.fda.gov/drugsatfda_docs/psg/Budesonide%20and%20Formoterol%20fumarate%20dihydrate_MDI_021929_RC06-15.pdf

Case Study: Proposed Non-Q2 Test Formulation

- Proposed test formulation is Q1 the same, but not Q2 the same as the RLD

	Test	RLD	%Difference between T and R
Excipient A	T	R	> 5%

- Proposed level for excipient A did not exceed previously FDA-approved drug product intended for inhalation – There's no safety concern.
- Submitted all in vitro studies, in vivo PK studies on both strengths and a comparative clinical endpoint study on the lowest strength as recommended in the PSG
- Additional in vitro sensitivity studies to evaluate the impact of varying amount of Excipient A on aerosol performance
- Demonstrated the formulation understanding based on pharmaceutical development data, and elaborated how the proposed Test formulation was selected

Studies Submitted in Support of Non-Q2 Test Formulation

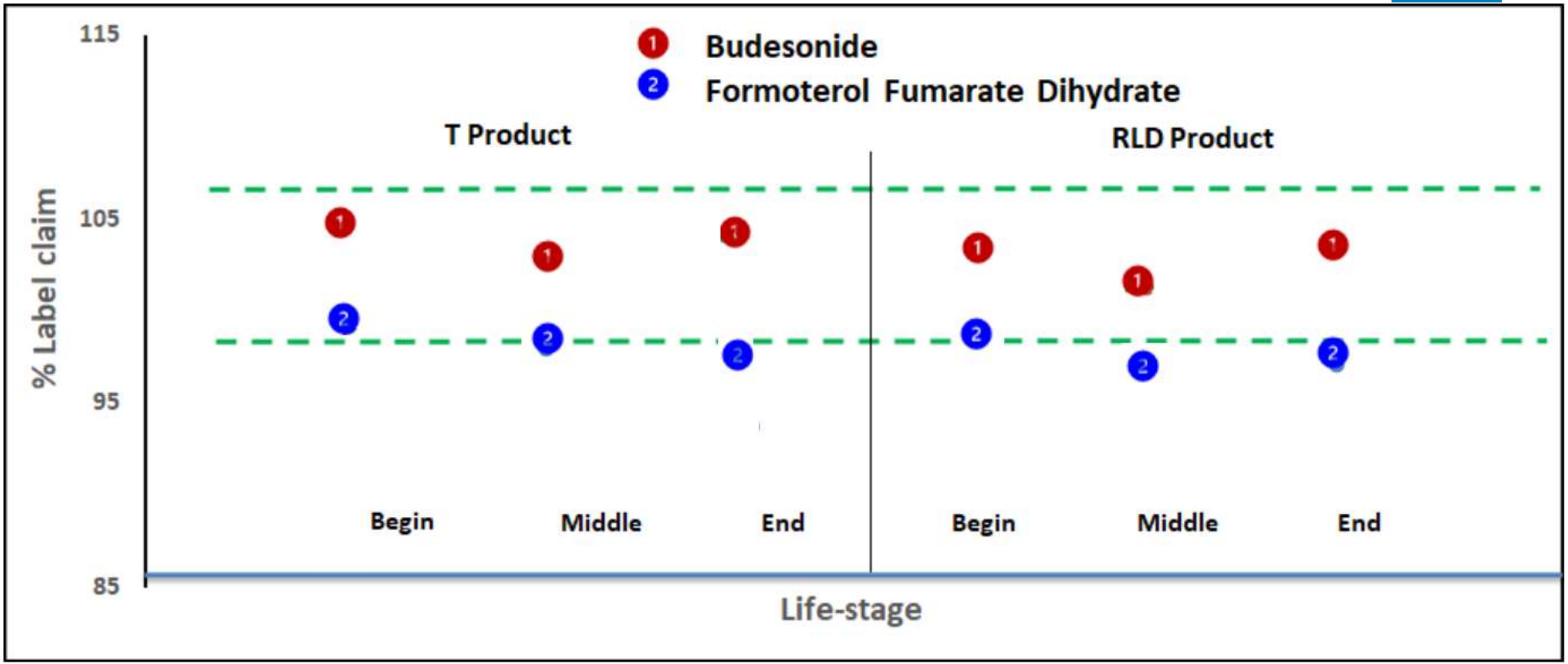
Sensitivity analysis studies	
SAC study on beginning (B), middle (M), and end (E) of unit life	**Conducted on the test product (with 3 levels: lower than T, Equal and higher than RLD of Excipient A) and compared with the RLD to evaluate the impact on aerosol performance** **3 batches/each Excipient A conc./ each product strength/ at least 10 samples from each batch to conduct Population Bioequivalence (PBE) analysis except for morphology characterization and suspension stability studies**
Priming and Repriming studies at B of unit life	
APSD study at B and E of unit life	
Spray Pattern & Plume Geometry studies at B of unit life	
Morphology Characterization by microscopy prior to actuation and following actuation	
Suspension Stability Study (to evaluate settling, creaming, or aggregation)	

Case Study: Outcome of Sensitivity Analysis

Varying amount of Excipient A did not affect product performance

Sensitivity analysis study	Parameter	Low Strength	High Strength
SAC at B, M, and E of unit life	Budesonide (BDS) and Formoterol Fumarate Dihydrate (FFD) amounts	Bioequivalent	Bioequivalent
Priming and Repriming studies at B of unit life		Bioequivalent	Bioequivalent
APSD study at B and E of unit life		Bioequivalent	Bioequivalent
Spray pattern at B of unit life	Ovality ratio and D_{max}	Bioequivalent	Bioequivalent
Plume geometry at B of unit life	Plume angle and width	Bioequivalent	Bioequivalent
Suspension stability: qualitatively similar among test formulations, formulation with varying amount of Excipient A and RLD			
Comparable morphology characterization: data by microscopy prior to actuation and following actuation			

Hypothetical Data: SAC Result As An Example



FDA NEWS RELEASE

FDA Approves First Generic of Symbicort to Treat Asthma and COPD

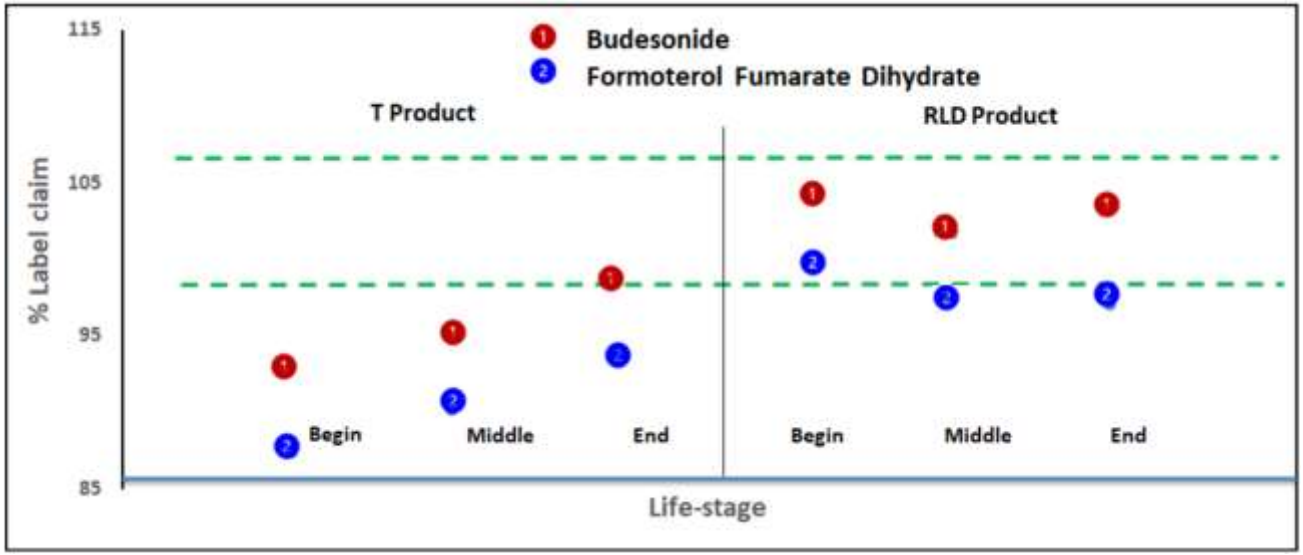
Agency Supports Development of Complex Generic Drug-Device Combination Product to Improve Competition and Access to More Affordable Medicines

Approved on March 15, 2022

www.fda.gov/news-events/press-announcements/fda-approves-first-generic-symbicort-treat-asthma-and-copd

General Consideration for a Proposed Non-Q2 Formulation

- A non-Q2 application may be submitted to FDA for OINDPs. However, sufficient data and information are needed to justify the impact of formulation differences on BE and safety.
- For example, if % drug label of the proposed non-Q2 formulation is consistently lower than that the RLD and fails to meet PBE analysis, an investigation should be conducted to determine whether this low delivery dose is caused by the difference in the formulation.



Summary

- FDA recommends using weight-of-evidence approach for establishing BE for locally acting OINDPs.
- Typically, a Q1/Q2 same formulation is recommended. Scientific justifications with appropriate data and explanation are recommended for the development of non-Q2 formulations.
- FDA provides multiple communication channels (such as control correspondences, product-development meetings, pre-submission meetings, mid-cycle review meetings, enhanced mid-cycle review meetings, post-complete response scientific meetings) at various stages to address industry's questions for generic drug development and regulatory approval.

Acknowledgement

- Partha Roy, Ph.D., Director, Office of Bioequivalence (OB)
- April C. Braddy, Ph.D., RAC, Division Director, OB/Division of Bioequivalence III
- Ke Ren, Ph.D., Deputy Division Director, OB/Division of Bioequivalence III
- Li Gong, Ph.D., Lead Pharmacologist, OB/Division of Bioequivalence III
- Fang Yuan, Ph.D., Senior Staff Fellow, Office of Lifecycle Drug Products/Office of Pharmaceutical Quality
- Bryan Newman, Ph.D., Lead Pharmacologist, Office of Research and Standards (ORS) /Division of Therapeutic Performance I (DTP I)
- Elizabeth Bielski, Ph.D., Senior Pharmacologist, ORS/DTP I
- Changning Guo, Ph.D., Supervisory Chemist, Office of Testing and Research/Division of Complex Drug Analysis

Poll Question #1

What are included in the FDA's weight of evidence approach for orally inhaled or nasal drug products?

A. Equivalent in vitro performance

B. Equivalent systemic exposure

C. Equivalent local delivery

D. Formulation and device sameness

E. All the above

Poll Question #2

How many types of OINDPs are available on the market?

A. Dry powder inhaler

B. Pressurized metered dose inhaler

C. Nebulizer

D. Soft mist inhaler

E. Nasal spray/Nasal aerosol

F. All the above


THANK YOU