



## An Overview of the FDA Position and Experience with the Equivalence of Respiratory Drugs

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**This presentation represents the personal opinions of the speaker  
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## Abbreviated New Drug Applications

- Drug products that are the same as a listed drug in:
  - active ingredient(s)
  - dosage form
  - strength
  - route of administration
  - labeling, including conditions of use
  - bioequivalence
- See 21 CFR 314.94(a) for details

## Definition of Bioequivalence

Pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions

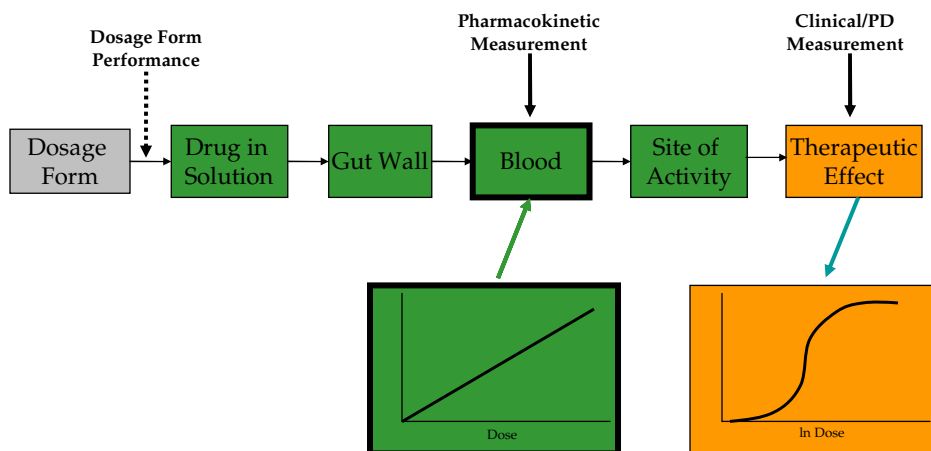
## Purpose of BE

- To confirm therapeutic equivalence (TE)
- Therapeutically equivalent products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring.
- The most efficient method of confirming TE is to assure that the formulations perform in an equivalent manner.

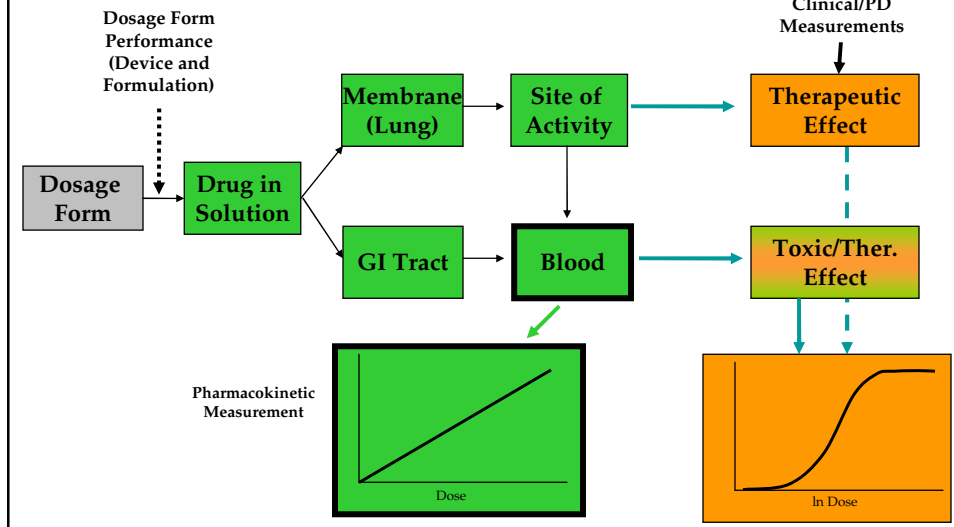
## Approaches to Determining Bioequivalence (21 CFR 320.24)

- In vivo measurement of active moiety or moieties in biologic fluid
- In vivo pharmacodynamic comparison
- In vivo limited clinical comparison
- In vitro comparison
- Any other approach deemed appropriate by FDA

## Model of Oral Dosage Form Performance



## Model of Inhalation Dosage Form Performance



## BE Recommendations: Formula Sameness

- Qualitative sameness ( $Q_1$ )
  - identical active and inactive ingredients as in the RLD
- Quantitative sameness ( $Q_2$ )
  - inactive ingredients within  $\pm 5\%$  of the concentrations in the RLD



## BE Studies for Locally Acting Inhalation Drug Products

- In vivo local delivery
  - Orally inhaled (solution; suspension)
  - Nasal (suspension)\*
- In vivo systemic exposure or systemic absorption
  - Orally inhaled (solution; suspension)
  - Nasal (suspension)\*
- In vitro
  - All (solution; suspension)
- **June 1999 Draft Nasal BA/BE Guidance**

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## Comparative In Vitro Tests # Batches and # of Units\*

- 3 batches of T and 3 batches of RLD
- 30 units of T
  - 10 units from each of the three batches
- 30 units of RLD
  - 10 units from each of the three batches
- \*Complete details provided in June 1999 *Draft Nasal BA/BE Guidance*

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## Data Analysis

- Clinical BE Studies
  - Analysis based on noncontinuous (categorical) endpoints or continuous endpoints?
- PD BE Studies
  - “Dose scale” analysis
- Systemic Exposure Studies (PK)
  - Two one-sided tests procedure (ANOVA)

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## Example: Oral Inhalation Aerosols (MDIs)

Albuterol MDI

**Local Delivery**

**Systemic Exposure/Absorption**

Formulation and Device

In Vitro Tests

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## Albuterol MDI Local Delivery BE

- Local Delivery Studies (PD Endpoints) - one of the following:
  - Bronchodilatation study
    - FEV<sub>1</sub> AUEC
    - FEV<sub>1 max</sub>
  - Bronchoprotection study
    - PD<sub>20</sub> or PC<sub>20</sub>

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## Albuterol MDI Local Delivery BE

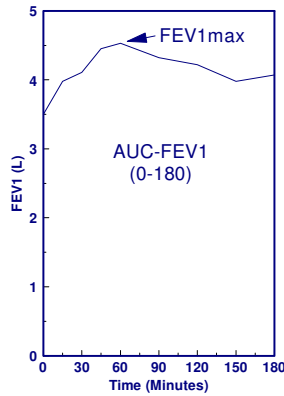
- Study Design
  - Randomized, crossover studies
- Treatments
  - Minimum
    - T1 T2, R1 R2
  - Preferred
    - T1 T2 T3, R1 R2 R3

***T = Test Product, R = Reference Product  
1, 2 & 3 = Number of actuations***

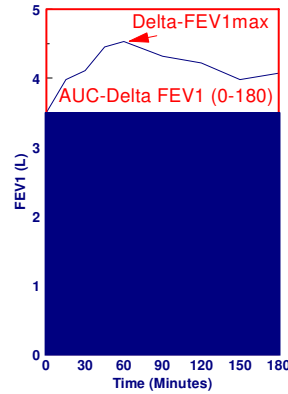
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## ALBUTEROL MDI LOCAL DELIVERY BE

- **BE Metrics based on FEV<sub>1</sub>**



Time (Min)	FEV1 (L)	Delta-FEV1 (L)
0	3.52	0.00
15	3.98	0.46
30	4.11	0.59
45	4.45	0.93
60	4.53	1.01
90	4.32	0.80
120	4.11	0.59
150	3.98	0.46
180	4.07	0.55



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GJPS 3/30/2000

## Albuterol MDI Systemic Absorption or Systemic Exposure BE

- Systemic Absorption
  - Cumulative dose single day regimen\*
    - 2, 4, and 6 actuations 30 min apart
    - Randomized, two-way crossover
    - Healthy nonasthmatics
    - Extrapulmonary effects only - BP, ECG, heart rate, serum potassium, serum glucose
- Systemic Exposure
  - PK (preferred): AUC and C<sub>max</sub>
- \* *January 1994 Interim Albuterol MDI Guidance*

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## Sources of Information

- OGD website:  
[www.fda.gov/cder/ob/default.htm](http://www.fda.gov/cder/ob/default.htm)
- Orange Book website:  
[www.fda.gov/cder/ogd/index.htm](http://www.fda.gov/cder/ogd/index.htm)
- FDA Guidance page:  
[www.fda.gov/cder/guidance](http://www.fda.gov/cder/guidance)
- 21 CFR: [www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=200221](http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=200221)
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