



Scientific and Regulatory Considerations for Bioequivalence (BE) of Dry Powder Inhalers (DPIs)

Sau (Larry) Lee, Ph.D.
Science Staff/Immediate Office
Office of Generic Drugs

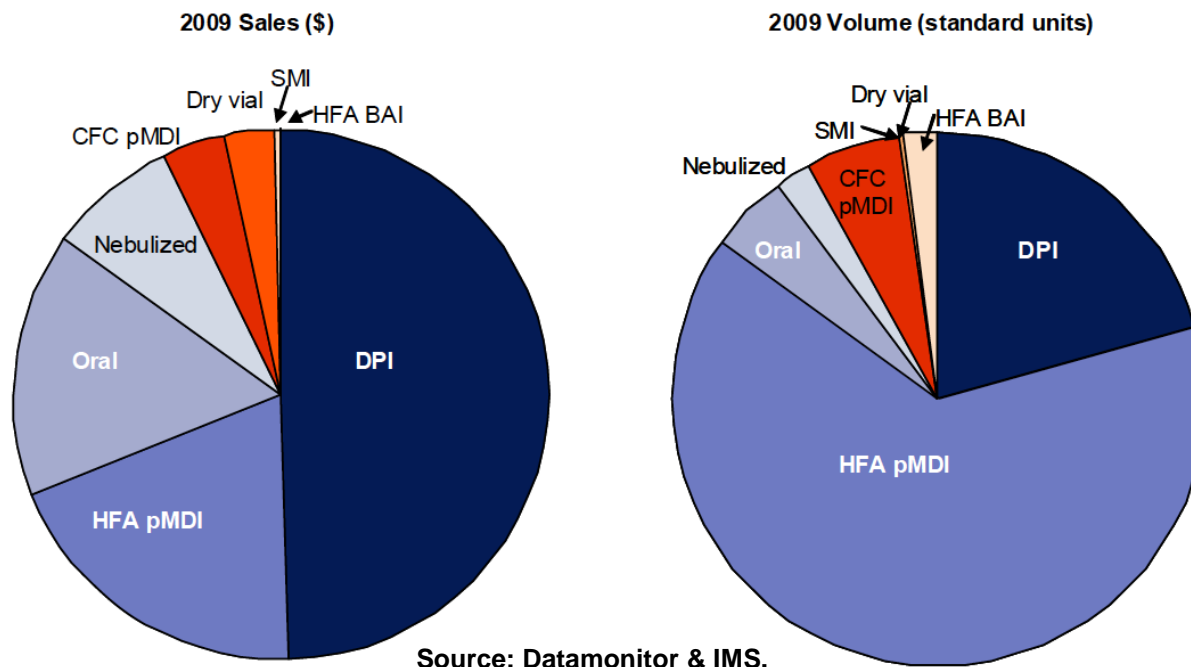
2011 GPhA/FDA Fall Technical Conference
October 4, 2011

This presentation reflects the views of the author and
should not be construed to represent FDA's views or policies

Outline

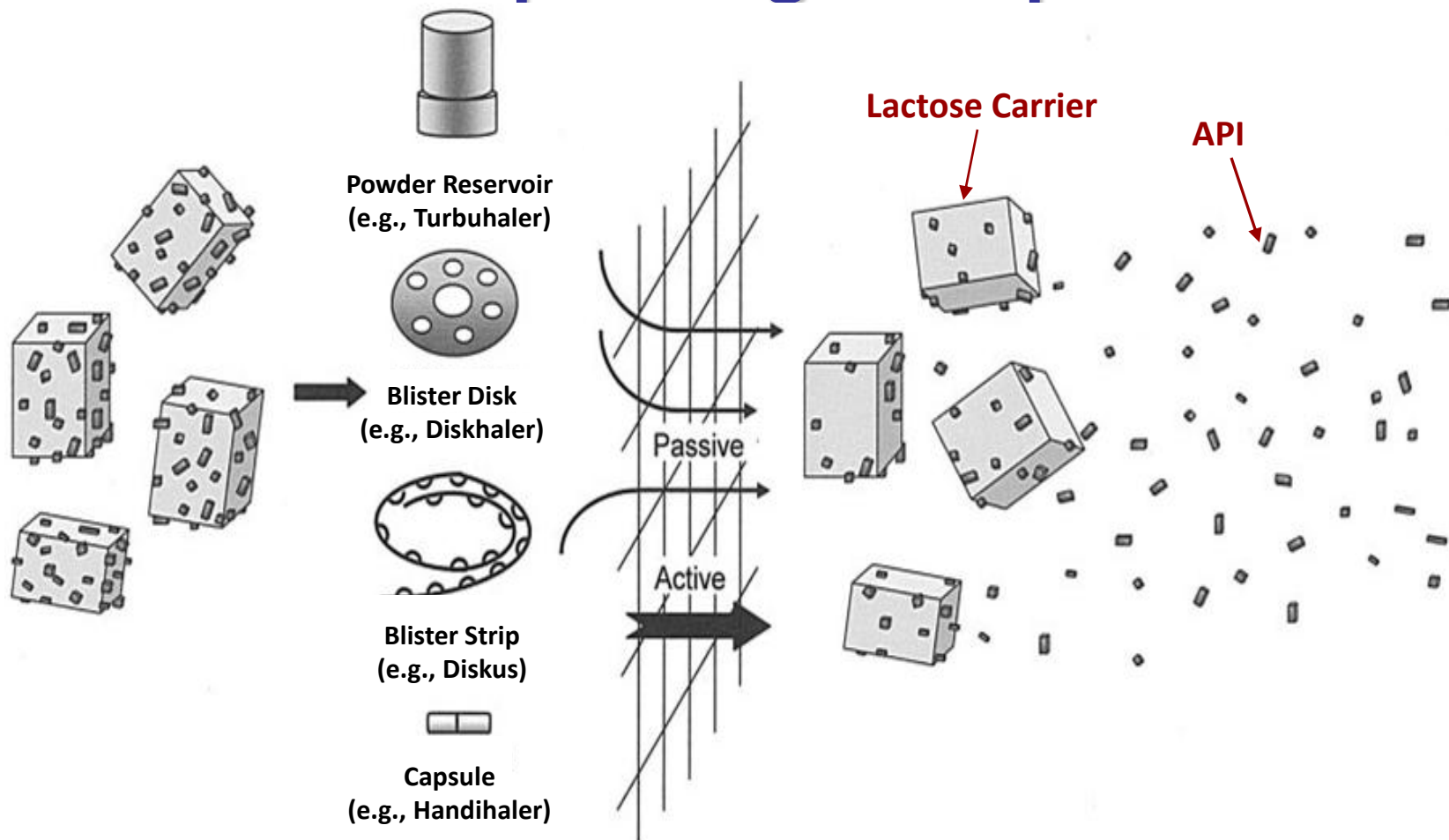
- Background of DPIs
 - Current landscape
 - Operating principle
- BE considerations for DPIs
 - Device and formulation
 - In vitro and in vivo studies
- Conclusions

Asthma/COPD: Sales value and volume by device/formulation



- DPIs make up nearly 50% of the market by sales value
- Popular among patients but only 21% of volume in the market is attributable to DPIs
- High sales driven by their relatively high price
- Need for generic DPIs

DPI Operating Principle



Formulation

Metering

Pulmonary delivery

Modified from Telko MJ, Hickey AJ. Respir Care 2005;50:1209-27

BE Considerations for Generic DPLs

Device and Formulation

- Similar size and shape
- Same basic operating principle
- Same number of doses
- Q1 and Q2

In Vitro Performance

- Equivalent emitted dose
 - 3 flow rates
 - B, M and E lifestages
- Equivalent APSD
 - 3 flow rates
 - B and E lifestages
- Comparable resistance

Equivalent Systemic Exposure

- Based on PK (AUC and Cmax) data
- For all strengths

Equivalent local delivery

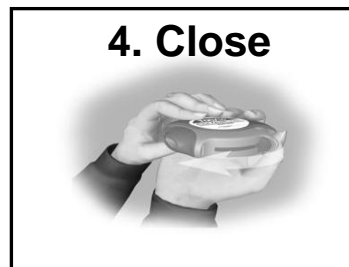
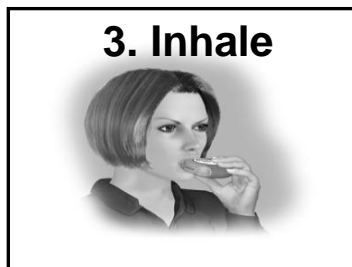
- Based on PD endpoints showing dose-response
- Dose-scale method

Device Considerations

- Ensure interchangeability in patient's hands
 - Same energy source for respiratory drug delivery
 - Passive (breath-actuated)
 - Same metering principle
 - Pre-metered single unit-dose (e.g., HandiHaler, capsule), pre-metered multi-unit-dose (e.g., Diskus, blister strip) or device-metered multi-dose (e.g., Turbuhaler, reservoir)
 - Same number of doses
 - e.g., 60 doses for Advair Diskus
 - Similar size and shape
 - Dose counter

Device Considerations

- Ensure interchangeability in patient's hands (Cont.)
 - Same basic external operating procedure
 - Four basic steps for Advair Diskus



- Effect of possible internal differences (e.g., geometry or dimension of air channels) on product safety and efficacy assessed by in vitro and in vivo BE studies

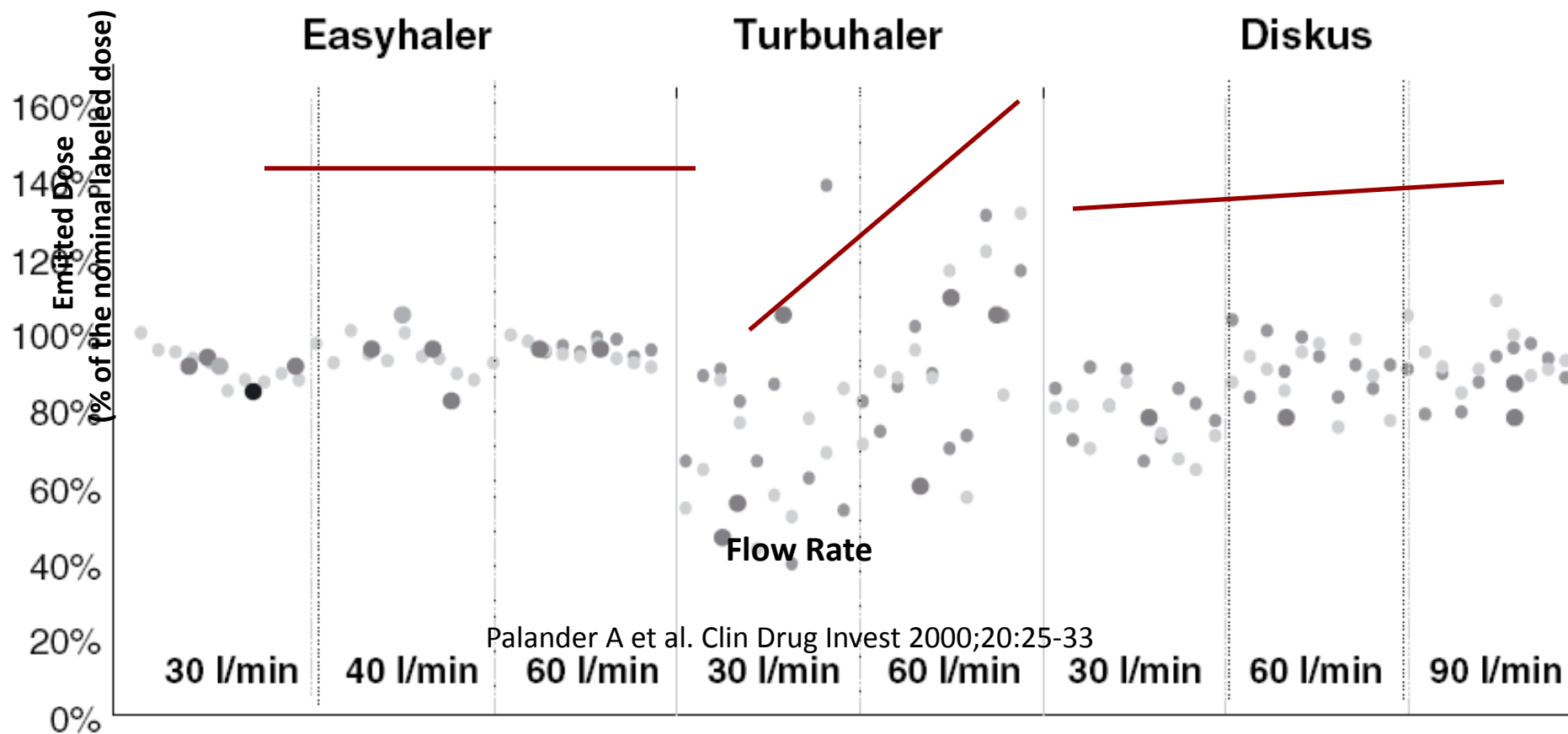
Formulation Considerations

- Qualitative (Q1) sameness
 - Same inactive ingredient(s)
 - Critical to establishing equivalence between the test and reference DPI products
 - Limited choices of inactive ingredients for DPIs
 - **Lactose** used in most DPIs (e.g., Flovent Diskus and Advair Diskus)
- Quantitative (Q2) difference permissible
 - Same inactive ingredient(s) but differ in concentration
 - Cannot exceed the levels used in other FDA approved products administered by the same route of administration (i.e., inhalation)
 - Effect of Q2 difference on the product safety and efficacy assessed by in vitro and in vivo BE studies
 - Submit pharmaceutical development data to support the selected test formulation

In Vitro Considerations

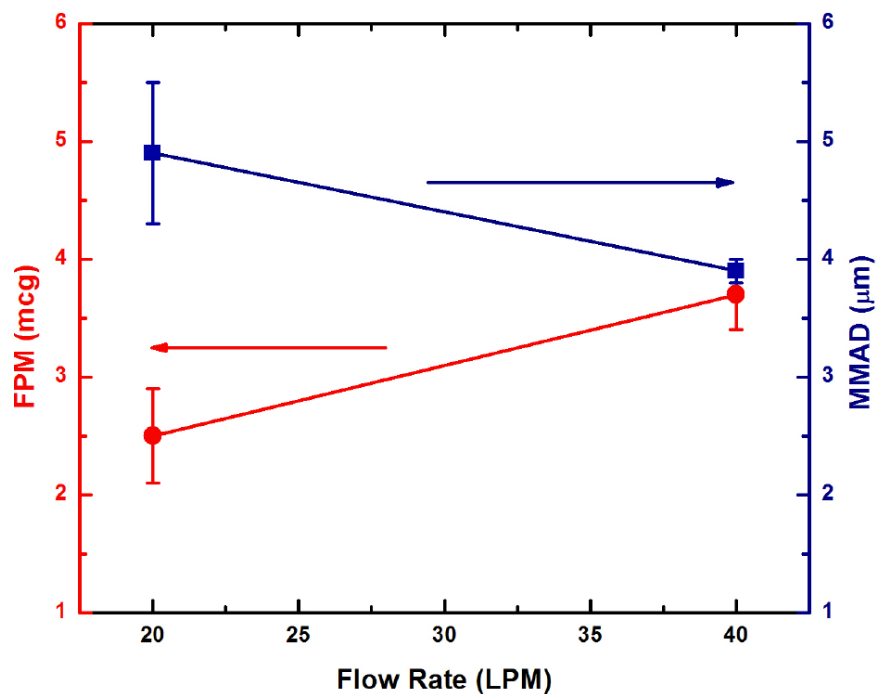
- Emitted dose (ED) and aerodynamic particle size distribution (APSD)
 - Critical attributes that are believed to affect the total and regional deposition of drugs in the lung, and therefore safety and efficacy of DPIs
- ED and APSD dependent on and sensitive to product- and process-related factors
 - Physicochemical properties of API(s) and carrier (e.g., particle size, shape and amorphous content)
 - Device properties (e.g., internal geometry and electrostatic charge)
 - Process conditions (e.g., material conditioning, micronization, and blending)

Effect of Flow Rate on DPI Performance

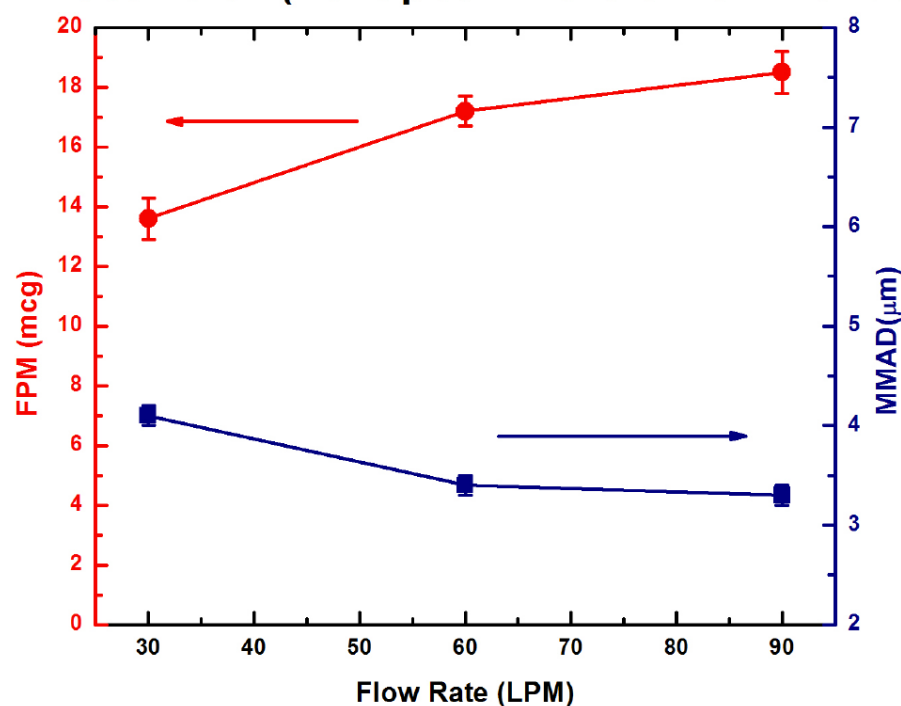


Effect of Flow Rate on DPI Performance

Handihaler



Accuhaler (European Version of Diskus)



Data from OGD research studies on DPIs

In Vitro Considerations

- Equivalent ED and APSD at various flow rates
 - Three different flow rates

Advair Diskus' Labeling

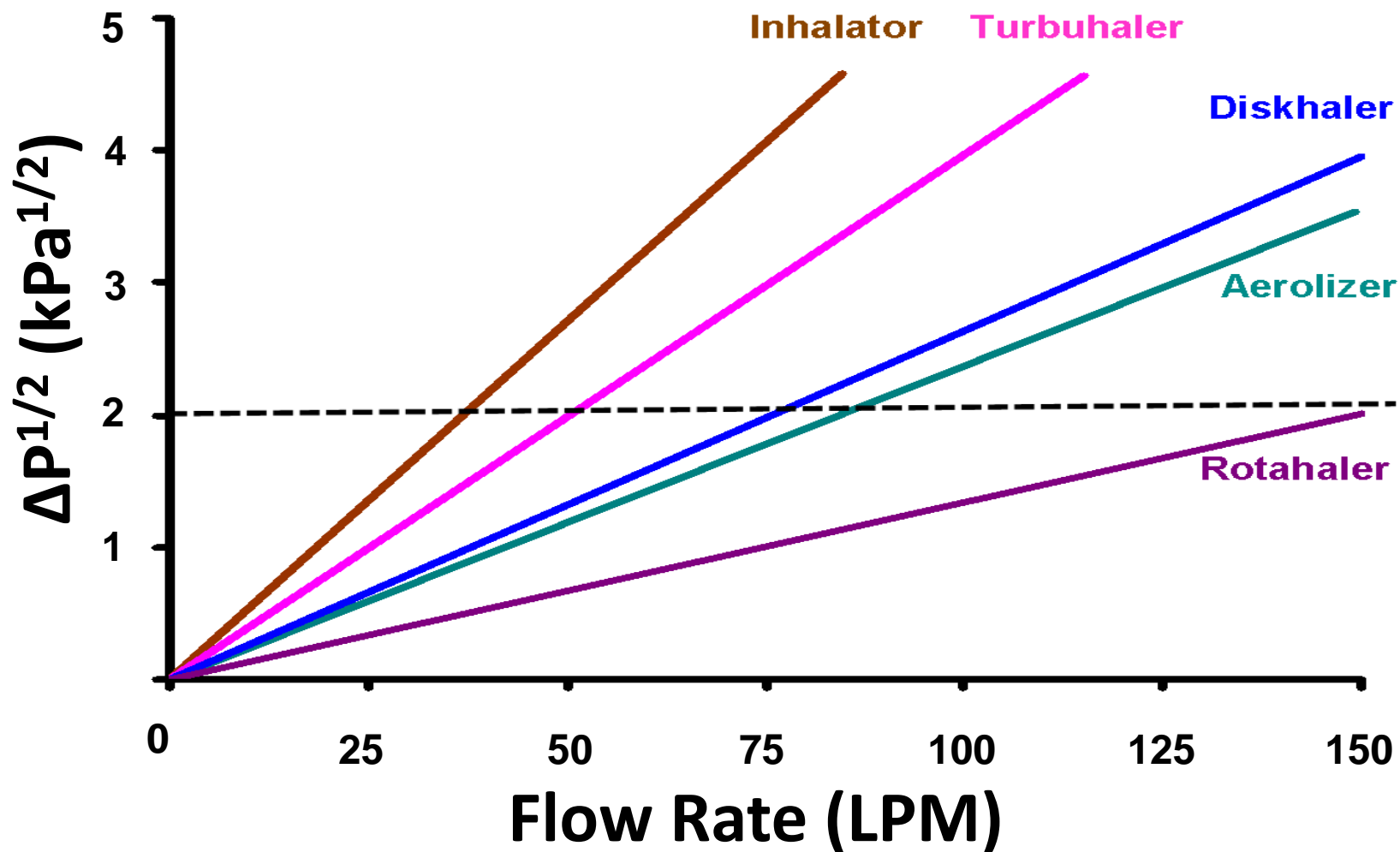
*"Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR DISKUS 100/50, 250/50, and 500/50, respectively, when tested at a flow rate of **60 L/min** for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean FEV1 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS inhalation device was 82.4 L/min (range, 46.1 to 115.3 L/min)"*

- For Advair Diskus, **30 LPM** (50% of labeled flow rate), **60 LPM** (labeled flow rate) and **90 LPM** (150% of labeled flow rate)
- Reasonably cover different inspiratory flow conditions generated by relevant patient population

In Vitro Considerations

- Equivalent ED at various lifestages
 - **Beginning**, **middle** and **end** lifestages for each of the three flow rates
 - e.g., for 60 dose Advair Diskus, beginning lifestage = 1st dose, middle lifestage = 30th dose, and end lifestage = 60th dose
 - Equivalence criteria
 - Population Bioequivalence (PBE)
- Equivalent APSD at various lifestages
 - **Beginning** and **end** lifestages for each of the three flow rates
 - Drug deposition on each individual site, to include the mouthpiece adapter, throat, preseparator, and each stage of the cascade impactor including the filter
 - Equivalence criteria
 - Impactor-sized mass (ISM) based on PBE
 - The CI profiles representing drug deposition on the individual stages of the CI.

Device Resistance = $\Delta P^{1/2}$ /Flow Rate

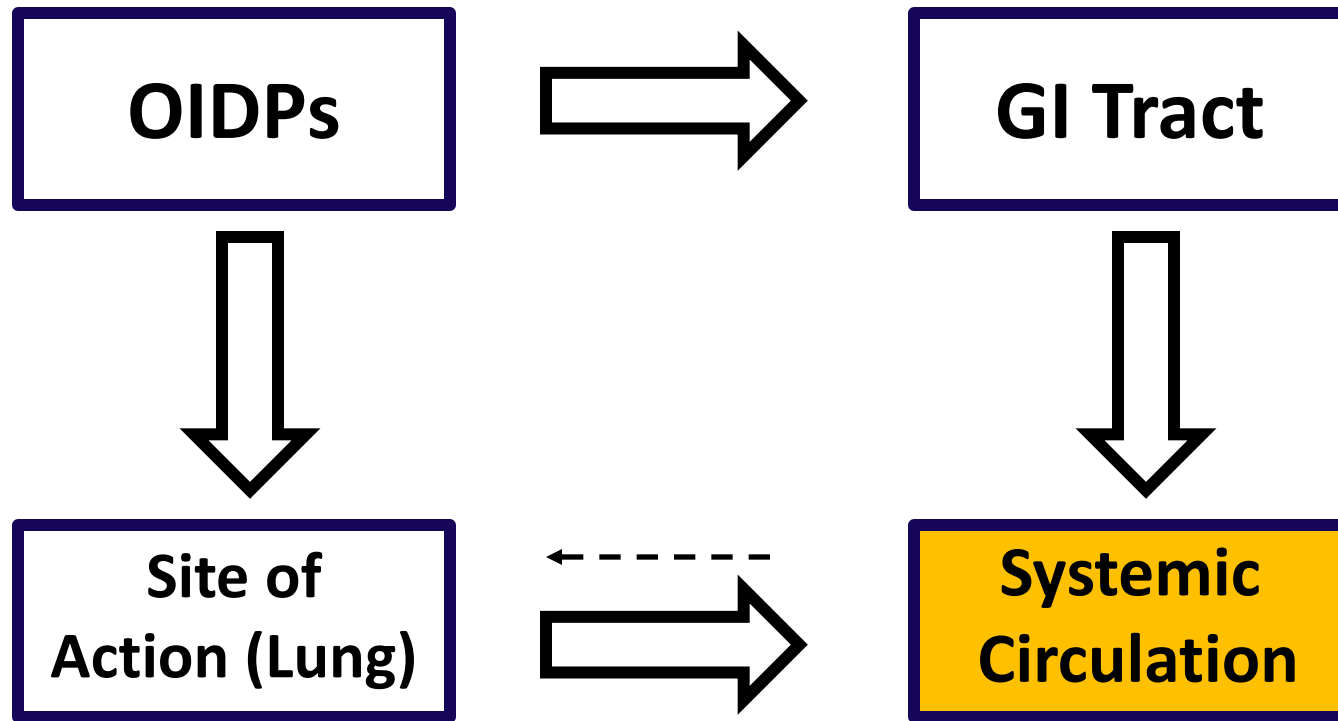


Modified from Clark AR et al. J Aerosol Med 1993; 6 (2), 99-110

In Vitro Considerations

- Comparable device resistance between the test and reference device
 - Patient compliance
 - Ensures that the targeted patient population is able to operate the test device effectively and receive proper medication **without any significant change in their inspiratory effort**
 - Increase the likelihood of establishing equivalence of ED and APSD
 - Potential impact on the dependence of ED and APSD on flow rate

Pharmacokinetics (PK) of Orally Inhaled Drug Products (OIDPs)



The sampling site for PK studies (plasma) is a compartment that is downstream of the site of action (the lung)

Equivalent Systemic Exposure

- PK BE study design
 - Single-dose studies in healthy subjects
 - Dose based on minimum number of inhalations and justified by assay sensitivity
 - PK measurements feasible for inhaled fluticasone propionate (ICS) and salmeterol (LABA) (LLOQ = 1 pg/mL)¹
- Equivalence criteria
 - 90% CI: 80% – 125% for AUC and C_{max}
- No PK BE study waiver of low strengths
 - The relationship among PK dose proportionality across multiple strengths, in vitro performance (i.e., ED and APSD) and product characteristics (e.g., formulation) not well understood for DPI drug products

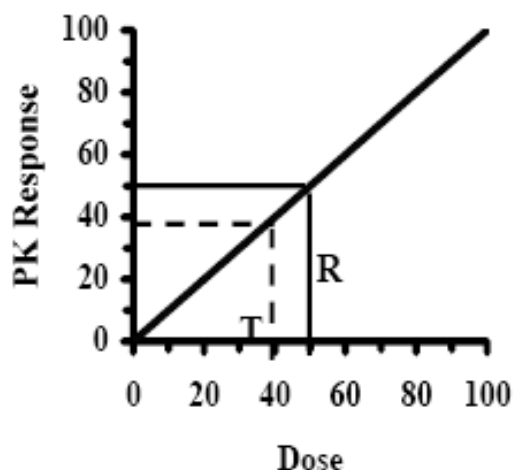
¹Harrison et al. J Aerosol Med Pul Drug Del. 24:1-8, 2011

Equivalent Local Delivery

- PD study endpoints in asthmatic patients
 - Exhaled nitric oxide (eNO) endpoint for ICS
 - Bronchodilatation or bronchoprovocation endpoint for LABA
- Establishment of dose-response
 - Ensures the sensitivity of a pharmacodynamic (PD) study to distinguish potential differences between test and reference products
- Dose scale method for equivalence
 - E_{\max} model
 - Equivalence based on “dose scale”

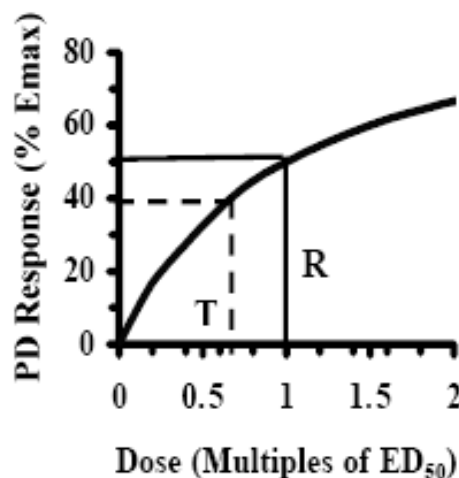
Dose-Response Relationships

PK Studies



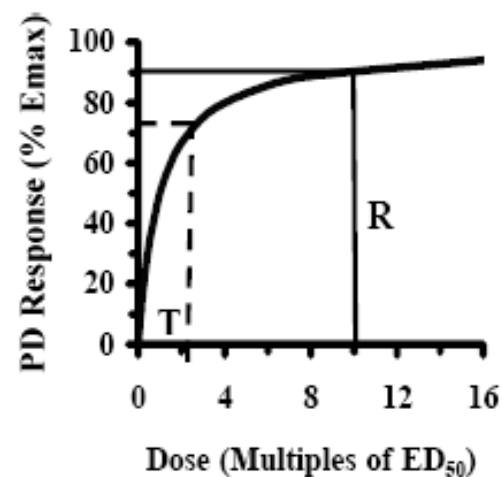
Response Scale T/R: 0.80
Dose Scale: 0.80

PD Study (Ref Dose = ED_{50})



Response Scale T/R: 0.80
Dose Scale: 0.67

PD Studies (Ref Dose > ED_{50})

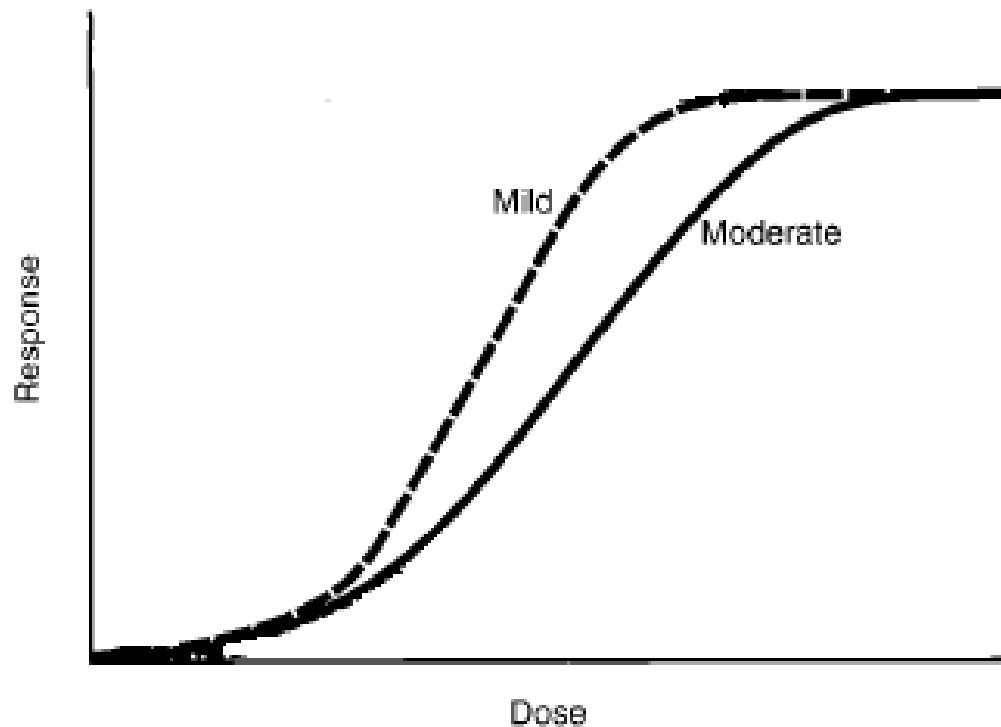


Response Scale T/R: 0.80
Dose Scale: 0.26

ED_{50} = Dose required to produce 50% of the fitted maximum PD response

Singh et al. RDD 2005:115-126

Asthma Severity and Dose-Response



Different theoretical dose-response curves to inhaled corticosteroids

PD BE Study Design for ICS Based on eNO: Points to Consider

- A randomized, double-blind, multiple-dose, crossover dose-response study
 - Use of double dummy to blind to product and dose
 - 3 doses of R and 1 dose of T
 - 3 doses of R for Flovent: 50 mcg x 1, 50 mcg x 2 and 50 mcg x 3
 - 3 doses of R for Advair; 100/50 mcg, 250/50 mcg and 500/50 mcg
- Pilot study encouraged to identify
 - Washout and dosing intervals
 - Within subject variability
 - Subject screening criteria for study enrichment
 - PD metric (e.g., AUEC)
 - Dose response
 - Variability

Reference Scaling Approach to Bioequivalence Intervals

- Scaling of the dose scale BE interval to the within-subject variability of the RLD in the study
 - $< 30\%$ (no scaling)
 - BE limits = 80 – 125%
 - $\geq 30\%$ (scaling)
 - BE limits expand in proportion to RLD product variability
- Requires replication of the reference treatment
 - A second administration of R at the same dose as T
- Development of reference scaling approach for the dose-response PD studies underway

Conclusions

- BE assessment of DPIs takes into account
 - Device and formulation
 - In vitro drug product performance
 - in vivo studies of local delivery and systemic exposure

Acknowledgements

- OGD
 - Wallace Adams
 - Bhawana Saluja
 - Feiyan Jin
 - Stephanie Kim
 - Robert Lionberger
 - Bing Li
 - Dale Conner
 - Lawrence Yu
- DPARP
 - Badrul Chowdhury
 - Lydia Gilbert McClain
 - Susan Limb