

## Use of In Vitro vs In Vivo Data To Conclude Equivalence of Two Inhaled Products (A CMC Perspective)

**Dave Parkins**  
**Director DPI Product Development**

EUROPEAN EQUIVALENCE CONSIDERATIONS FOR ORALLY  
INHALED PRODUCTS (OIPS) FOR LOCAL ACTION.  
Frankfurt, October 2010

### Overview

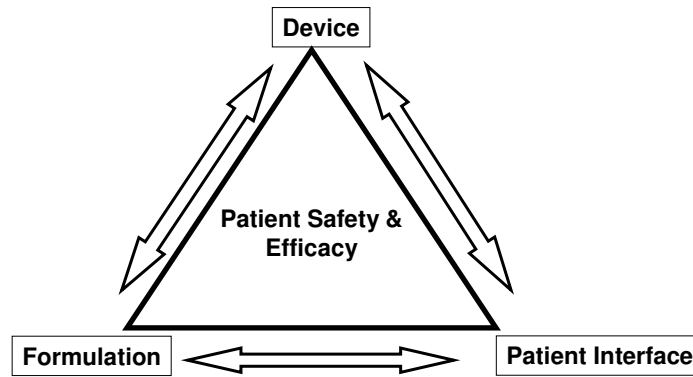
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- Review MDI design factors relevant to product performance
- Review Literature examples of MDI bioequivalence investigations
- Review DPI design factors relevant to product performance
- Review Literature examples of DPI bioequivalence investigations
- Using DPI case study
  - consider CMC aspects of device equivalence & the role of the in-vitro test

Input for  
Track C “In-vitro only equivalence”  
Track D “Device Design Similarity”

## Inhaled Product Design

Safety/Efficacy dependent on formulation, device and use in hands of patient



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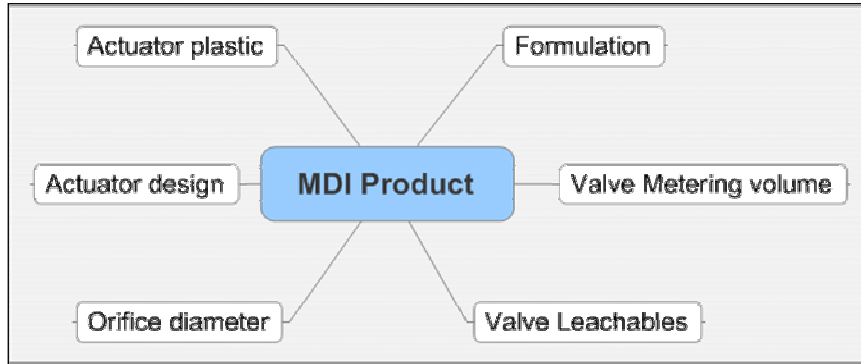
## Metered Dose Inhalers



- MDIs are complex systems requiring integration of formulation, valve, can and actuator
- May be used with ancillary devices eg Spacer

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## MDI Design Factors



### Areas for consideration

- Impact of formulation & design differences
- Timing of plume - e.g. co-ordination of inhalation manoeuvre
- Changes in mouth feel – e.g. perception of dose received, impact on inhalation manoeuvre

## Literature examples of MDI bioequivalence investigations

Example	Pk (Charcoal Block)	Efficacy	Product changes	In-vitro measure
Beclomethasone innovator CFC MDI vs Beclomethasone generic CFC MDI	Equivalent (No Charcoal Block)	Equivalent	Design & formulation differences ?	CI Profile FPM < 5.8µm, FPM<3.3µm
Fluticasone HFA MDI vs Fluticasone CFC MDI	Not Equivalent at all dose strengths (No Charcoal Block)	Equivalent	Design differences & Formulation change	FPM < 5µm
Beclomethasone CFC MDI vs Beclomethasone HFA MDI	Not Equivalent (No Charcoal Block)	Not Equivalent	Design & formulations differences	CI Profile FPM < 5.8µm, FPM<3.3µm
Flunisolide CFC MDI vs Flunisolide HFA MDI	Not Equivalent (No Charcoal Block)	Not Equivalent	Design inc spacer Solution vs suspension	median particle size
Fluticasone /Salmeterol innovator HFA MDI vs Fluticasone /Salmeterol generic HFA MDI **	Not Equivalent Charcoal Block	-	Design & formulation ? differences	Stage groupings s0,s1,s2, s3-5,s6-7, FPM
Salbutamol reference CFC free MDI vs Salbutamol generic MDI***	Equivalent (No Charcoal Block)	-	Design & formulation ? differences	Stage groupings Th., s0-2,3-5,6-F Stages S3,s4,s5,s6,s7,F

Adapted From Daley-Yates, Respiratory Drug Delivery 2010, 1, 273 – 281

\*\* Clearie et al, B J Clin Pharmacol. 2010, 69, 6, 637 – 644

\*\*\* Case Study A. Fuglsang, PQRI workshop Orlando April 30, 2010

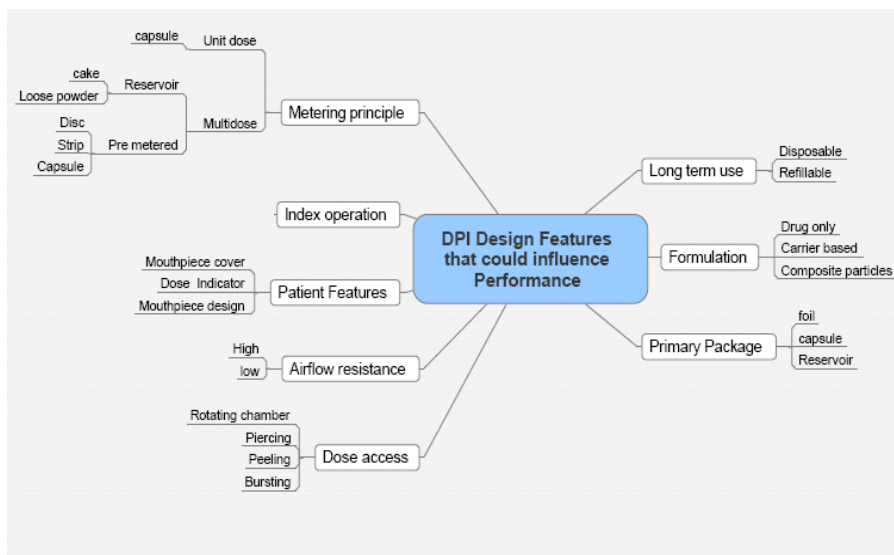
## Dry Powder Inhalers



There is a significant diversity in the design of DPIs  
Reliance on inspiration to achieve aerosolisation and drug delivery

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## Diversity in Dry Powder Inhaler Design



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## Literature examples of DPI bioequivalence investigations

Example	Pk (Charcoal Block)	Efficacy	Product change	In-vitro measure
Budesonide Turbuhaler® Vs Budesonide Flexhaler®	Equivalent (No Charcoal Block)	Not Equivalent	reservoir vs reservoir Modified mouthpiece Counter added Addition of lactose	Emitted Dose data @ 60l min Flexhaler has improved dose consistency
Budesonide Turbuhaler® Vs Budesonide Easyhaler®	Equivalent (Charcoal Block)	Equivalent	reservoir vs reservoir Different design/shape Addition of lactose*	No in-vitro data PIFR was 45 & 60l/min @ 4kPa
Fluticasone Propionate Diskus® Vs Fluticasone Propionate Diskhaler®	Not Equivalent ( in Healthy ) Close match (in Asthmatics) (No Charcoal Block)	Equivalent	Metered dose vs metered dose Different design/shape Blend concentration	Fine Particle Mass & < 2um
Salmeterol/Fluticasone Propionate Diskus® Vs Salmeterol/Fluticasone Propionate RPID®	Not Equivalent (No Charcoal Block)	Equivalent	Metered dose vs reservoir Different design/shape Same formulation	ED & Stage data @ 60l/min FPM

Adapted From Daley-Yates, Respiratory Drug Delivery 2010, 1, 273 – 281

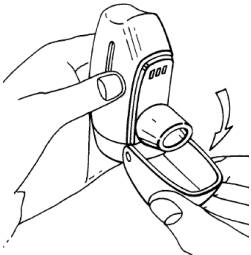
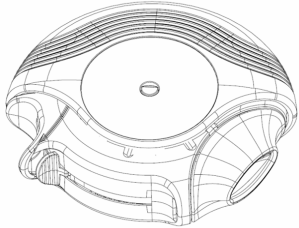
\* from PIL

## DPI Device Design Case Study

- Aim: To determine the efficacy, safety, pharmacodynamic & in-vitro performance of 2 Salmeterol 50mcg/Fluticasone Propionate 250mcg DPIs
  - In-vitro assessment of emitted fine particle mass profiles by CI
  - 12 week clinical efficacy/safety study in subjects with asthma to assess clinical equivalence
  - Pharmacokinetic/pharmacodynamic study in adult asthmatics to determine equivalence of drug delivery & systemic exposure

Daley-Yates et al, Clinical Therapeutics, vol 31, Number 2, 370–385, 2009.

## RPID and Diskus® Designs

	Reservoir Powder Inhalation Device	Diskus®
Product Strength	Salmeterol 50µg /Fluticasone Propionate 250µg	
Active Pharmaceutical Ingredient	Micronised Fluticasone Propionate & Salmeterol Xinafoate	
Carrier/Diluent	Lactose Monohydrate	
Blend/ Unit dose	13mg	
Manufacturing Process	Blend & Fill	
Metering Principle	Reservoir	Premetered
Device airflow resistance	Typically 2.5 kPa @60/min	
Device Design		

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## Summary APSD Data for RPID and Diskus®

		RPID	Diskus
<b>Fluticasone Propionate</b>			
Total Dose	Mean (µg)	231.8	231.4
	Range (% mean)	92 - 110	98 - 102
Stages 1 - 5 (0.6 - 6.2 µm)	Mean (µg)	66.8	66.2
	Range (% mean)	84 - 113	95 - 105
<b>Salmeterol</b>			
Total Dose	Mean (µg)	46.5	46.6
	Range (% mean)	90 - 110	98 - 102
Stages 1 - 5 (0.6 - 6.2 µm)	Mean (µg)	13.1	12.8
	Range (% mean)	87 - 112	94 - 107

ACI @ 60l/min

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## Clinical Efficacy / Safety Study

12 week multi centre double blind, double dummy, study in 270 moderate asthmatics (age 12+)

Primary efficacy parameter – mean morning PEF

### Key Findings

- 95% CIs for mean morning PEF lay within +/- 15L/min
- No notable differences in specific adverse events/ adverse event profiles

Two delivery devices considered clinically equivalent in terms of morning PEF, well tolerated with comparable safety profiles.

## In-vivo systemic Pharmacokinetics / Pharmacodynamics

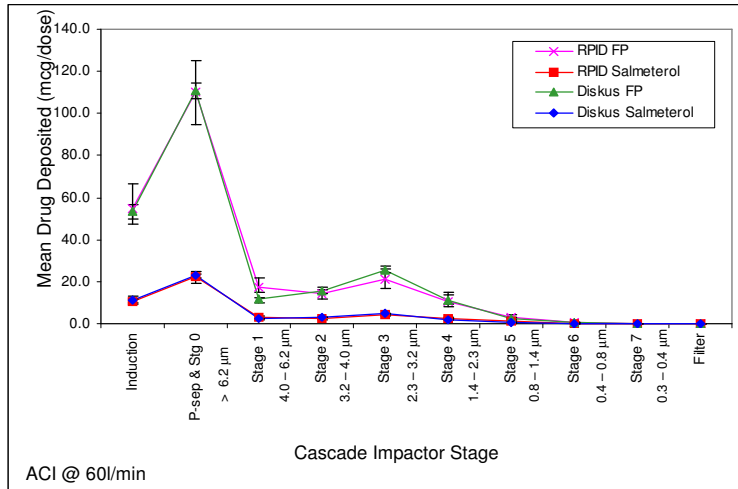
Single Centre double blind, double dummy, 14 day crossover study in 22 adults with moderate asthma.

### Key Findings

- Systemic FP exposure 2-fold greater with RPID  
Estimated ratio  $AUC_{\tau} = 2.00$  (90% CI: 1.56 - 2.55)
- Systemic Salmeterol exposure almost 2-fold greater with RPID  
Estimated ratio for  $C_{max,ss} = 1.92$  (90% CI: 1.64 - 2.25)

Two delivery devices could not be assumed to be bioequivalent for Delivery of Fluticasone Propionate and Salmeterol

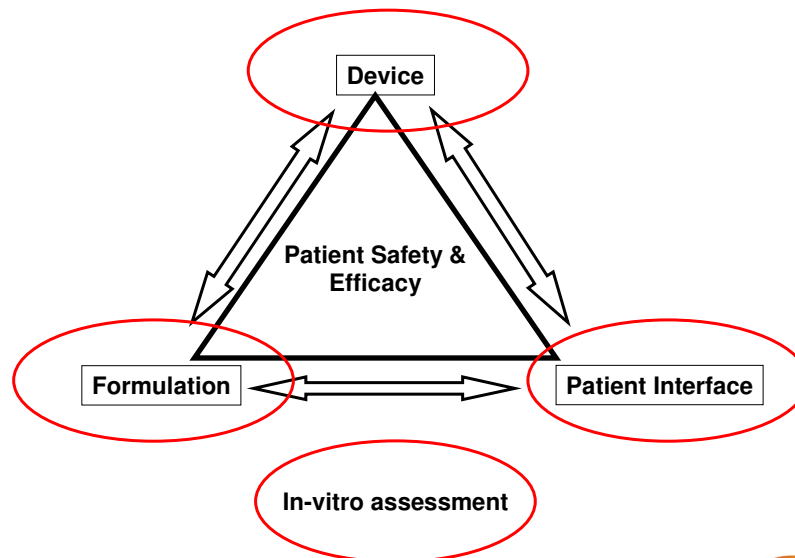
## In-Vitro Test - RPID /Diskus CI Profile



Difference in profile appears not enough to explain 2 fold increase in systemic exposure


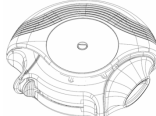
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## Why did we observe the difference ?



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## Difference in Formulation / Device Design ?

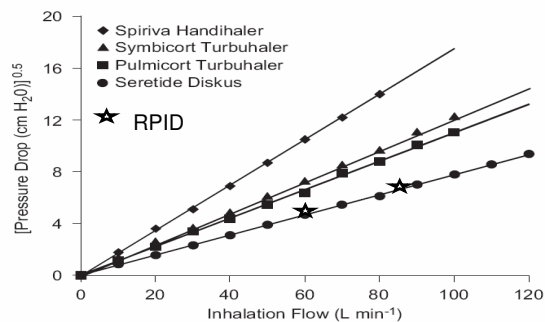
	Reservoir Powder Inhalation Device	Diskus®
Product Strength	Salmeterol 50µg /Fluticasone Propionate 250µg	
Active Pharmaceutical Ingredient	Micronised Fluticasone Propionate & Salmeterol Xinafoate	
Carrier/Diluent	Lactose Monohydrate	
Blend/ Unit dose	13mg	
Manufacturing Process	Blend & Fill	
Metering Principle	Reservoir	Premetered
Device airflow resistance	Typically 2.5 kPa @60/min	
Material of construction	Polymer composition similar	
Device Design		

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## Flow Rate Dependency

- Main attribute of a DPI inhaler that controls flow rate is device resistance
- Device Resistance =  $\frac{\text{Flow Rate}}{\sqrt{\text{Measured Pressure Drop}}}$



- Which approach to flow rate dependency?  
30/60/90L/min vs pressure drop vs patient relevant flow rates

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## RPID Comparative Performance at 2 flow rates

		60L/min	85L/min
Fluticasone	Emitted Dose (ug)	231.8 (93%)	250.5 (100%)
	Fine Particle Dose <5µm (ug)	58.2	57.8
	MMAD (µm)	3.2	3.5
	GSD	1.6	1.7
Salmeterol	Emitted Dose (ug)	46.5 (93%)	48.9 (98%)
	Fine Particle Dose <5µm (ug)	11.6	11.9
	MMAD (µm)	2.9	3.2
	GSD (µm)	1.6	1.7

## In-Vitro Test - Limitation of the in-vitro test ?

Cascade testing is a Quality Control Test



Test conducted under fixed conditions

Difference in deposition mechanisms

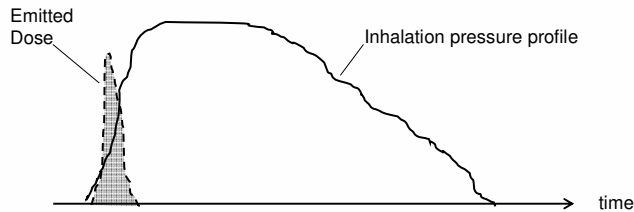
In-vitro - deposition is by impaction

in- vivo – deposition by impaction, sedimentation & diffusion.



Does not take into account how the patient interacts with the device

- Cascade methodology uses fixed high acceleration rates and profile does not reflect patient profiles

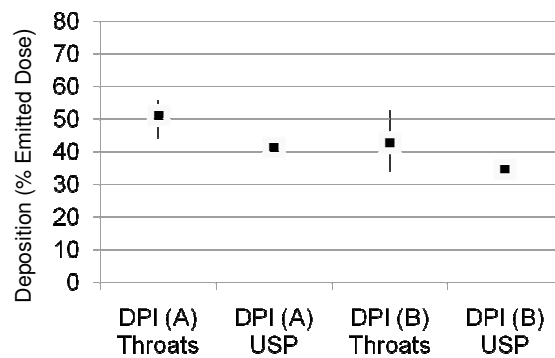


Schematic of emitted dose versus individual profile  
see Bisgaard et al Eur. Resp. J. 1998; 11; 111

- Device performance may be influenced by acceleration rate  
e.g. De Boer Int J Pharm 1997; 153; 67
- Timing of dose release may vary from DPI to DPI type  
e.g. Haughney et al Resp. Med, 2010; 104; 1237

## Predicting Oropharyngeal Deposition

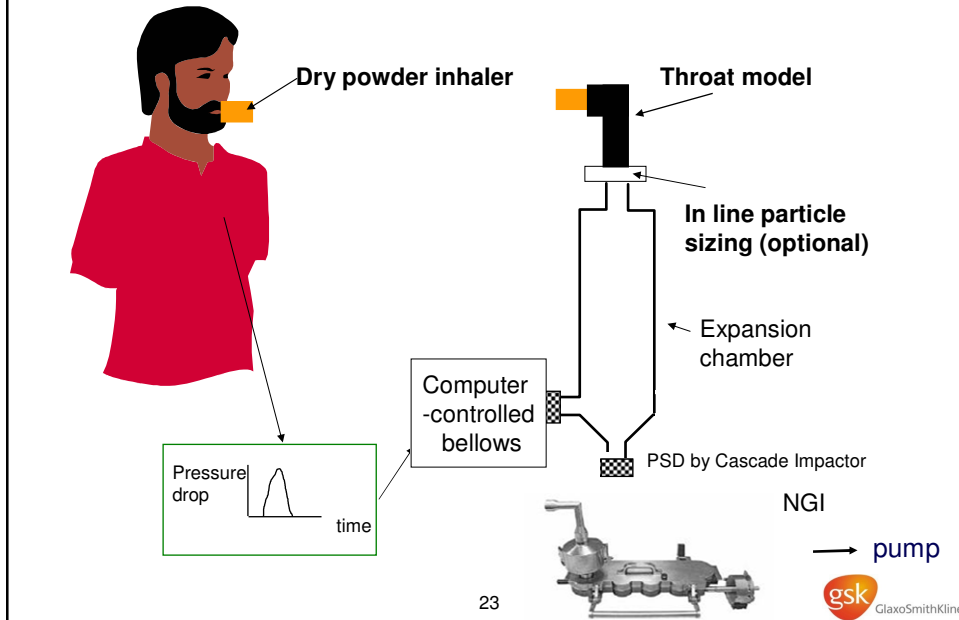
USP Induction port as predictor of throat deposition



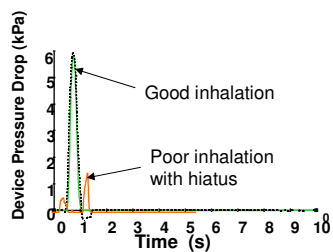
Adapted from Burnell et al, J Aerosol Med, 20(3), 269, 2007

See also  
Dolovich et al J. Aerosol Med., 11, S112-S115, 1998  
Newhouse et al, RDD VI, 1, 389, 1998  
Cheng et al, Aerosol Sci. Technol., 31, 286, 1999

# Electronic Lung



- Lung dose is dependent on
- Patients' mouth-throat size
  - Age - paediatrics different to adults
  - Patients' inhalation manoeuvre
  - Disease state



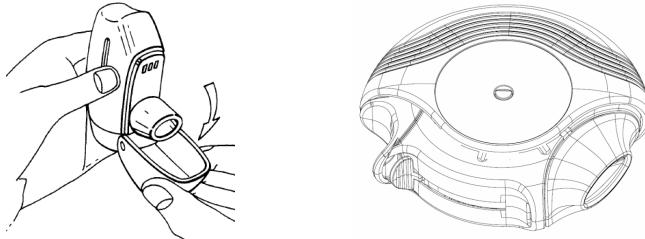
Adult throat models

- consideration of inspiratory effort required ?

see Prime D. Determining Flow and Flow Acceleration Conditions for *In-Vitro* Testing of Dry Powder Inhalers' J. Aerosol Med. (2005) 18, 119

## Difference in Device / Patient Interface

Design Differences influenced way patient interacted with device in ways not detected by the in-vitro test ?



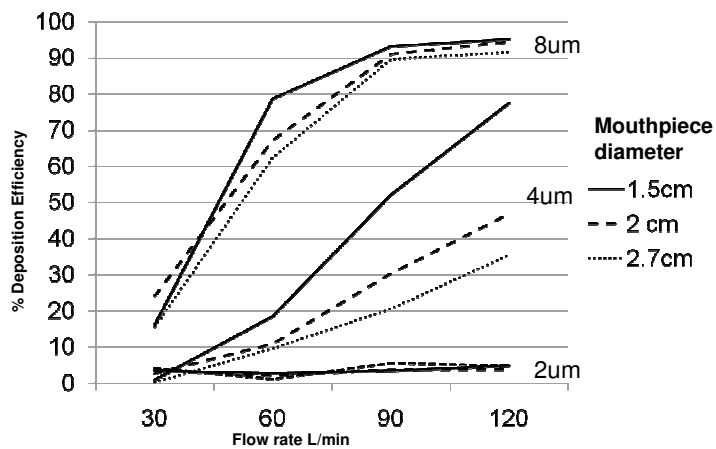
Mouthpiece design influences how wide mouth is opened during inhalation – potential to impact deposition efficiency in-vivo.

Potential to affect airflow within oral cavity – leading to differences not seen by in vitro method ?

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## Impact of mouthpiece diameter on deposition efficiency

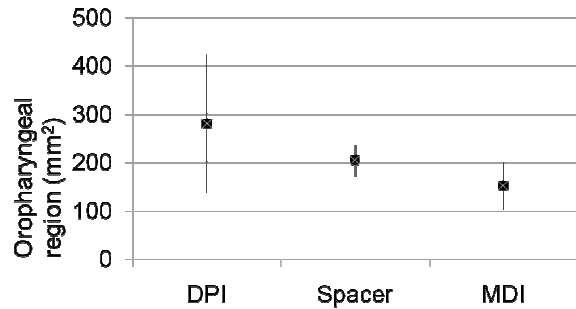


After Lin et al, J Aerosol Med. 2001, 14(3) 269

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## Influence of device on Oropharyngeal cross section



Adapted from Entezazi et al, J Aerosol Med, 17(4), 325, 2004

- Likely factors include device resistance, tongue position, patient effort
- Deposition in oropharyngeal region impacts lung deposition

## Difference in Device / Patient Interface - Patient Handling

- Correct operation and inhalation technique key to therapeutic outcome
- Diversity of design means critical steps varies from device to device  
eg Fink et al Respir. Care, 50, 1360, 2005
- Handling studies show that rates of patient/device critical errors can vary from device to device  
eg Khassawneh et al Respir. Care, 53, 324, 2008,  
Molimard et al J.Aerosol Med., 16, 249, 2003
- Common mishandling errors for DPIs is for Patient to inhale unnecessarily slowly eg Melani et al, Ann.Allergy Asthma Immunol. 93, 439, 2004
- Whilst instruction leaflet not sole source of training, patients do find it useful  
eg Melani et al, Ann.Allergy Asthma Immunol. 93, 439, 2004

## Summary

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- From a CMC perspective establishing in-vitro/in-vivo correlations requires numerous factors to be addressed
  - Formulation, device design, patient interface, limitations of the CI test
- Studies reported in the literature contain limited CMC information
  - Limited / inconsistent reporting of in-vitro performance
  - Limited information on formulation & device differences
  - Studies often include both formulation & device changes
- Track C “in-vitro” equivalence
- Track D Device Design Similarity