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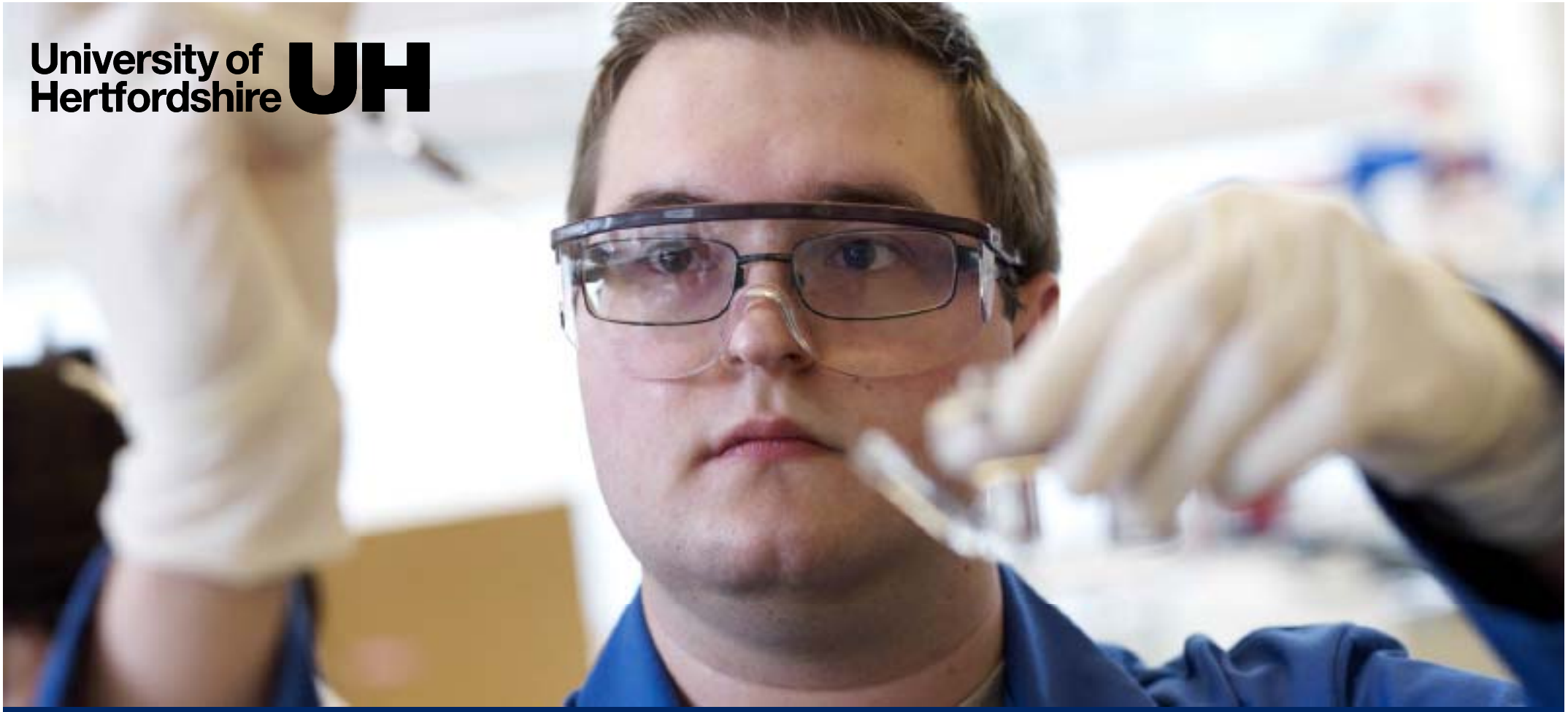

Equivalence Testing of Inhalation Products

Darragh Murnane

Centre for Research in Topical Drug Delivery & Toxicology

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On 30 March 2015, the Academy of Pharmaceutical Sciences and The Aerosol Society held an academic-industrial workshop to develop a roadmap for in vitro equivalence research.

"Bioequivalence of Orally Inhaled Drug Products: Establishing the Scientific Basis for Regulatory Acceptance of In Vitro Strategies"

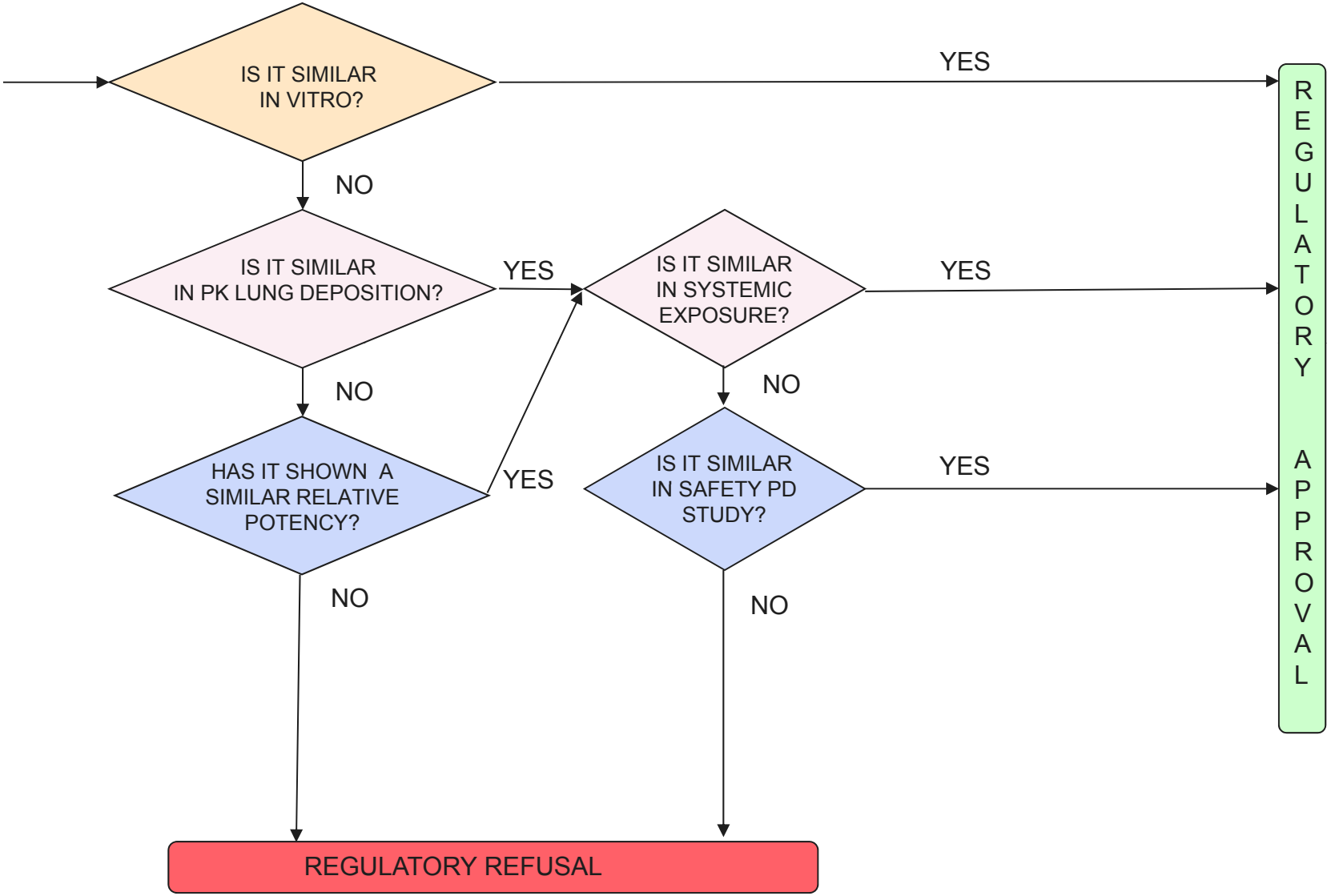
Some contents of this lecture include information presented by speakers at the workshop including: **Dr Alfredo García-Arieta** (AEMPS, Spanish regulator); **Dr Burak Ozsogut** (Neutec R&D); **Dr Peter Daley Yates** (GlaxoSmithKline); **Prof. Robert Price** (University of Bath), & **Dr Philippe Rogueda** (Aedestra Consulting).

Their contribution is acknowledged at the outset of this talk, and their slides are acknowledged when they appear.

Principles of Topical Inhaled Bioequivalence

The Stepwise Approach to Demonstration of Equivalence

A decision-tree logic



The marketing approval context

Examples of UK ‘Generic’ products (courtesy of Philippe Rogueda)

Salbutamol
- 3 pMDI
- 6 DPI

Formoterol fumarate
- 1 pMDI
- 4 DPI

Beclomethasone dipropionate
- 2 pMDI
- 4 DPI

Budesonide
- 7 DPI

- Most of the approved products were actually filed as branded products not true generics
- Their interchangeability for all patients is not guaranteed

A selection of EMA-approved ‘equivalent’ products

Dry powder inhalers offer a specific challenge (Philippe Rogueda)

Product	In vitro BE	PK/PD Studies	PIF Studies
Rolenium	✗	4	✓
Seroflo pMDI	✗	2	✓
Airflusal	✗	5	✓
DuoResp	✗	11	✓
Formoterol DPI	✓	✗	✓

Key Factors Determining Drug Delivery to Pharmacologic Target Sites in the Lung

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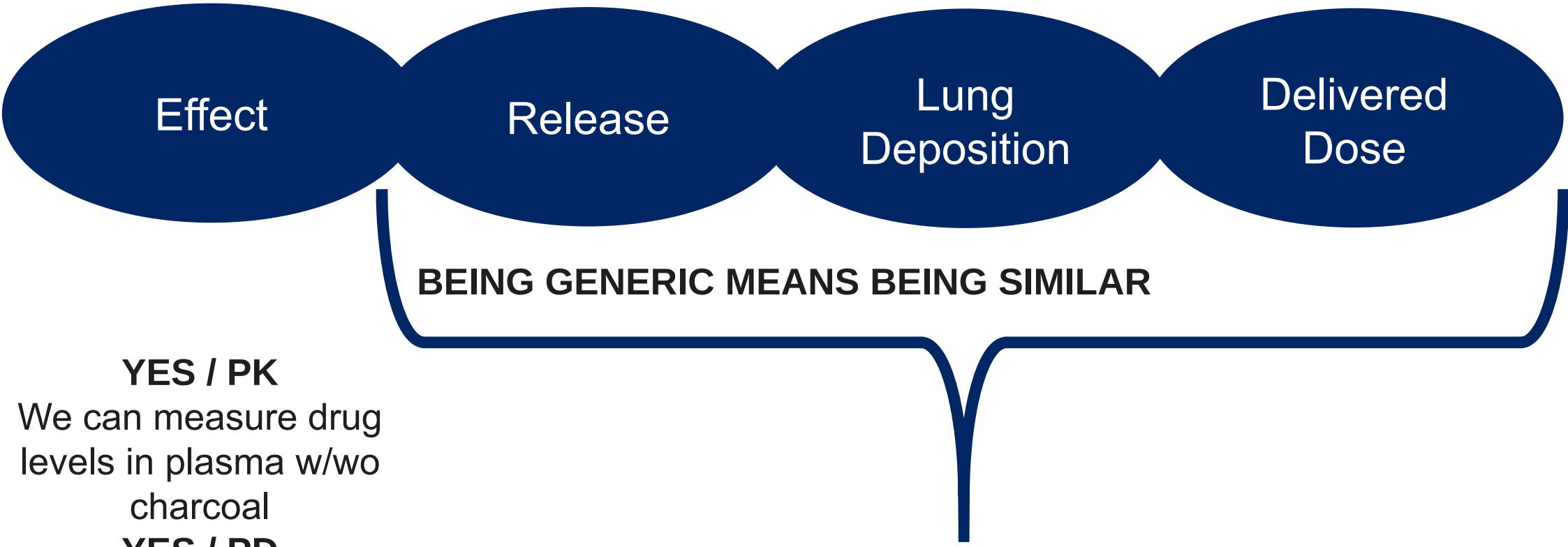
Assessing the evidence base for stepwise approaches (B Ozsogut)

Justifying the use of *in vitro* data to demonstrate equivalence



YES / PK
We can measure drug levels in plasma w/wo charcoal

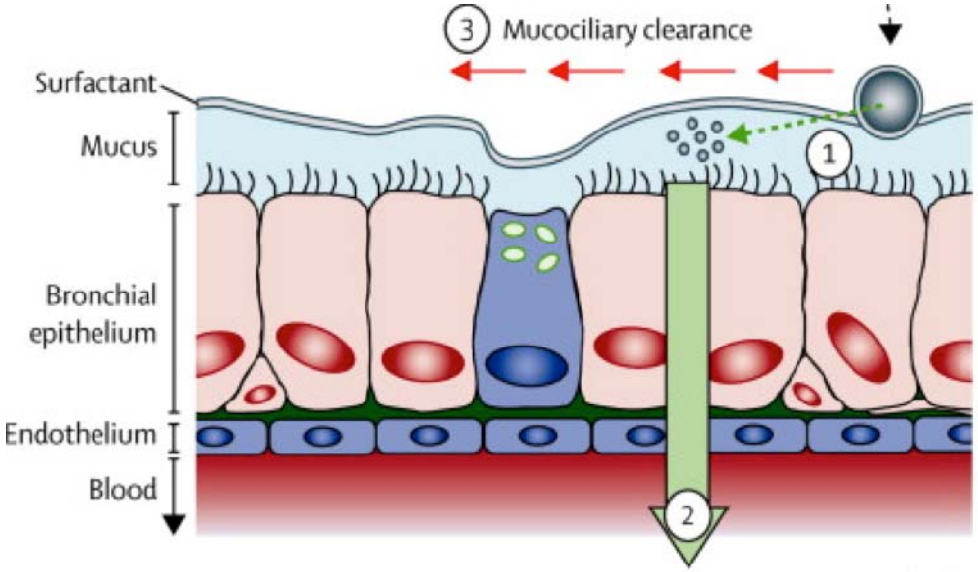
YES / PD
We can measure efficacy

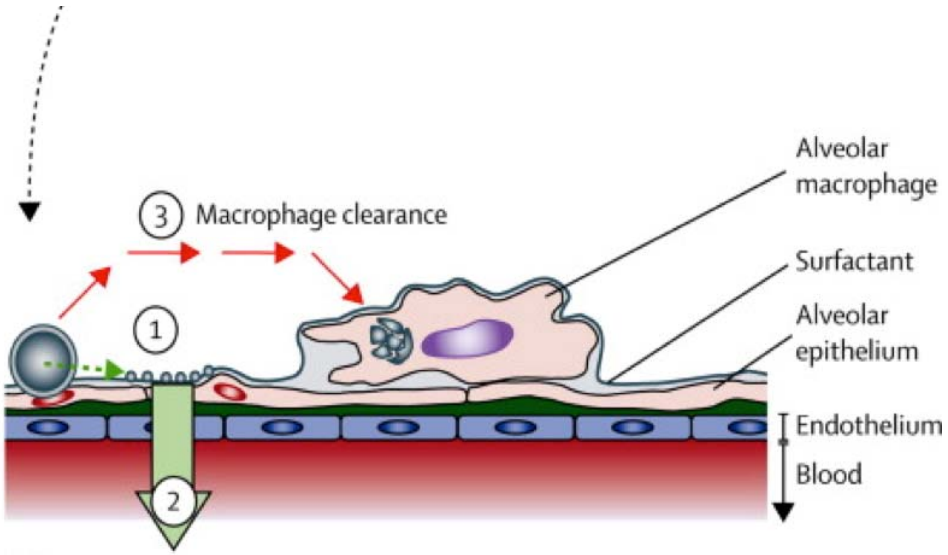
SCOPE FOR *IN VITRO* EQUIVALENCE TESTING
What methods can be indicative of lung deposition, API release and transport to the receptors or systemic circulation

Key factors determining drug delivery to local target sites

Where does the drug go and how will this affect absorption?

- **Dose**
  - Dose released from device and delivered to the lung
  - Dose released from device that reaches the GI tract
- **Central vs. peripheral deposition**
- Different dissolution medium, clearance, different permeabilities





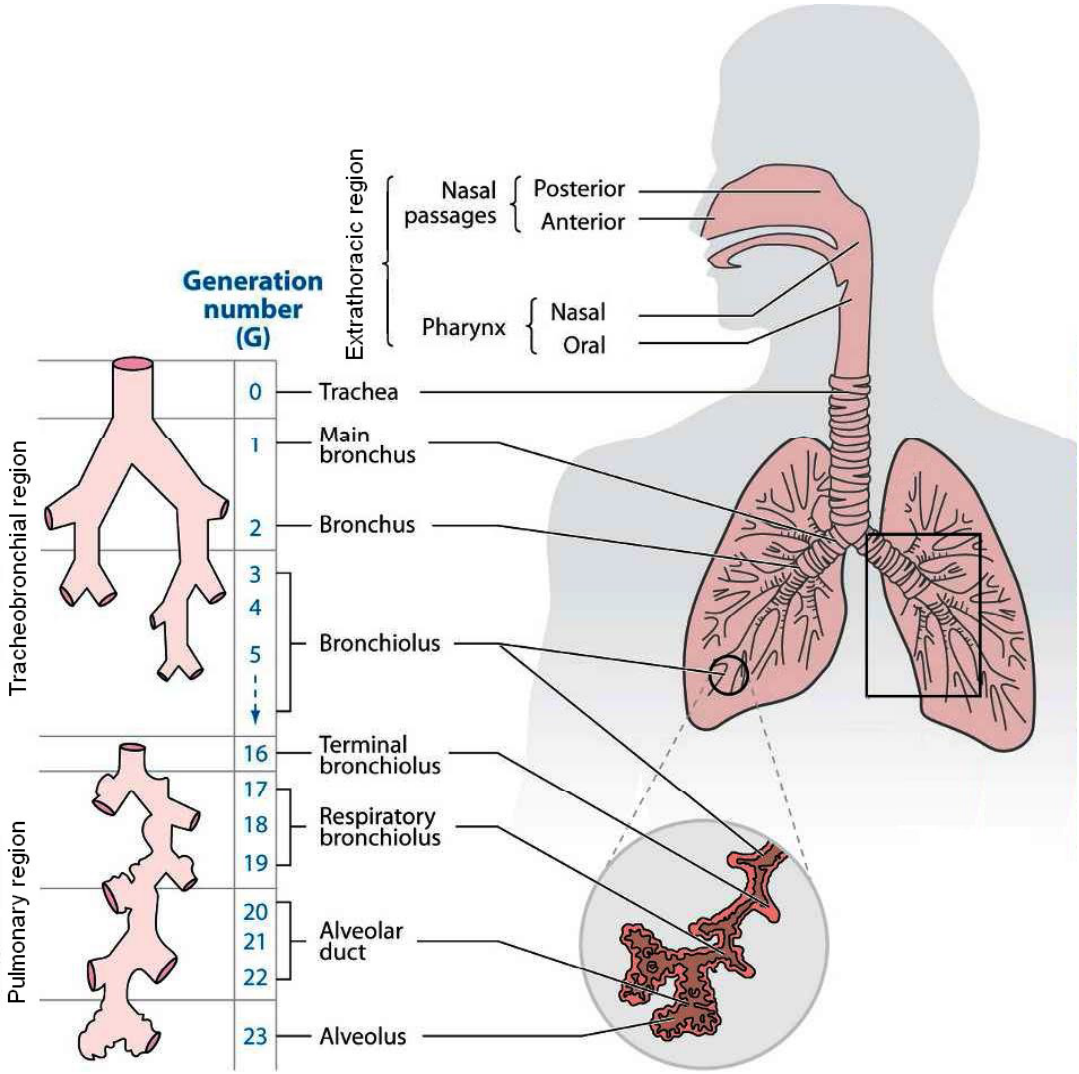
Key factors determining drug delivery to local target sites

The impact of particle size distribution on lung deposition sites

Particle Size > 6µm
Mostly - mouth/oral-pharyngeal deposition, high mucocilary clearance, and swallowed particles.

Particle Size 2 - 6µm
Mostly - upper/central airway deposition, some mucocilary clearance, systemic absorption

Particle Size < 2µm
Greater - peripheral airways /alveoli penetration, more exhaled, less deposition, less mucocilary clearance more systemic absorption



Hussain et al. theHealth 2011; 2(2):51-59

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In-Vitro Testing for Demonstration of Equivalence of Inhalation Products

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Assessing the evidence base for stepwise approaches

Justifying the use of *in vitro* data to demonstrate equivalence

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 22 April 2004
CPMP/EWP/4151/00

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POINTS TO CONSIDER ON THE REQUIREMENTS FOR CLINICAL DOCUMENTATION FOR ORALLY INHALED PRODUCTS (OIP)

DISCUSSION IN THE EFFICAY WORKING PARTY	September 2000
TRANSMISSION TO CPMP	January 2002
RELEASE FOR CONSULTATION	January 2002
DEADLINE FOR COMMENTS	April 2002
DISCUSSION IN THE EFFICACY WORKING PARTY	January 2004
TRANSMISSION TO CPMP	April 2004
ADOPTION BY CPMP	April 2004
DATE FOR COMING INTO OPERATION	October 2004

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 22 January 2009
Doc. Ref. CPMP/EWP/4151/00 Rev. 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE REQUIREMENTS FOR CLINICAL DOCUMENTATION FOR ORALLY INHALED PRODUCTS (OIP) INCLUDING THE REQUIREMENTS FOR DEMONSTRATION OF THERAPEUTIC EQUIVALENCE BETWEEN TWO INHALED PRODUCTS FOR USE IN THE TREATMENT OF ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN ADULTS AND FOR USE IN THE TREATMENT OF ASTHMA IN CHILDREN AND ADOLESCENTS

DISCUSSION AT THE EFFICACY WORKING PARTY	September 2000
TRANSMISSION TO CPMP	January 2002
RELEASE FOR CONSULTATION	January 2002
DEADLINE FOR COMMENTS	April 2002
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ADOPTION BY CPMP	April 2004
DATE FOR COMING INTO OPERATION	October 2004
DRAFT REV. 1 AGREED BY EFFICACY WORKING PARTY	September 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION REV. 1	18 October 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 April 2008
REV. 1 AGREED BY EFFICACY WORKING PARTY	January 2009
ADOPTION BY CHMP	22 January 2009
DATE FOR COMING INTO EFFECT	1 August 2009

Pharmaceutical properties and the need for a clinical programme

Examining the *in vitro* testing opportunities

Well Known Active Substance

The use of ONLY comparative *in vitro* data for this purpose is considered acceptable if;

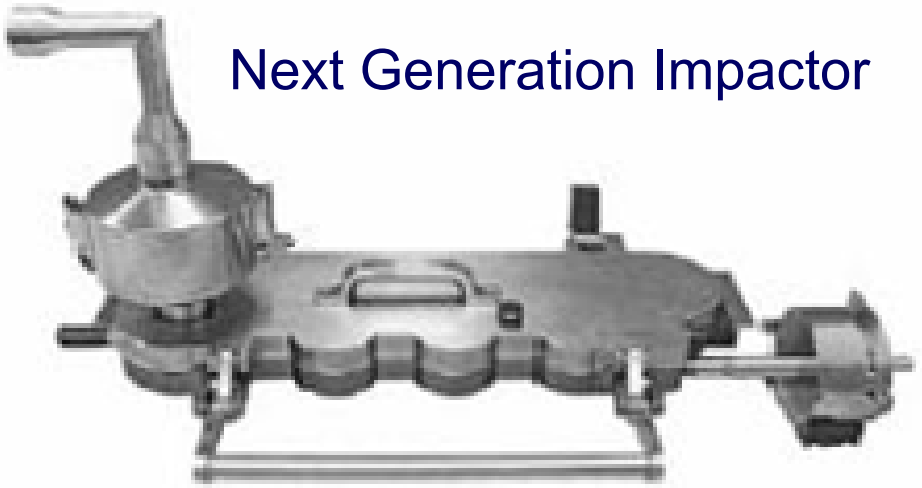
- ✓ the product contains the same active substance
- ✓ the physical state of the active substance is the same (dissolved or suspended)
- ✓ the pharmaceutical dosage form is the same
- ✓ any qualitative and/or quantitative difference in excipients should not influence the performance of the product, should not change the safety profile of the product,
- ? the target delivered dose should be similar (within +/- 15%)
- ? the qualitative and/or quantitative difference in excipients are known to have no influence on the deposition characteristics (e.g. Delivered Dose, FPD, MMAD, GSD) and on the inhalation behaviour of the patient (This should be justified for each excipient taking into account its amount.)
- ? the inhalation device has the same resistance to airflow (within +/- 15%)
- the inhalation device is identical in all parts which influence performance
- the inhaled volume through the device to enable a sufficient amount of active substance into the lungs should be similar (within +/- 15%)
- handling of the inhalation devices for the test and reference products in order to release the required amount of the active substance should be similar,

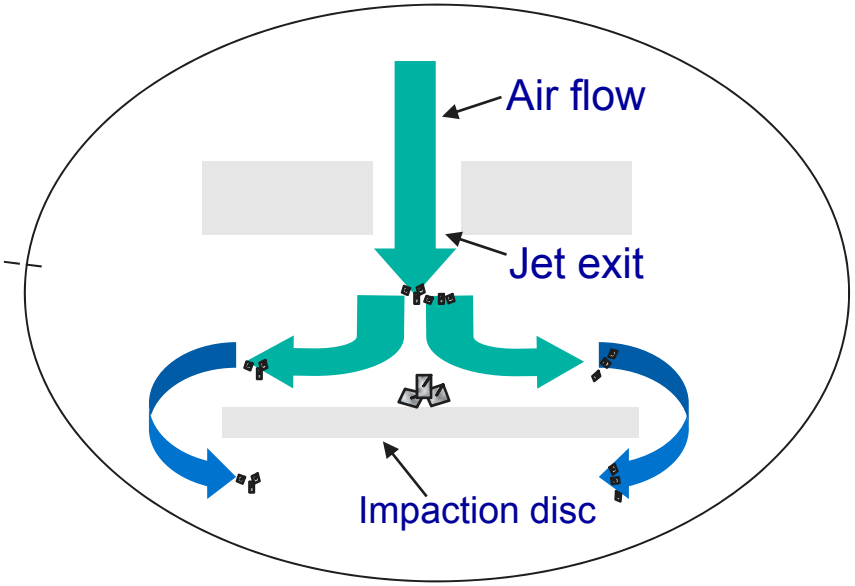
In vitro characterization techniques for delivered dose and size

Inertial impactors provide fine level size distribution data

Andersen Cascade Impactor

Next Generation Impactor





In vitro characterization techniques for delivered dose and size

A range of devices exist for assessment of inhalable dose

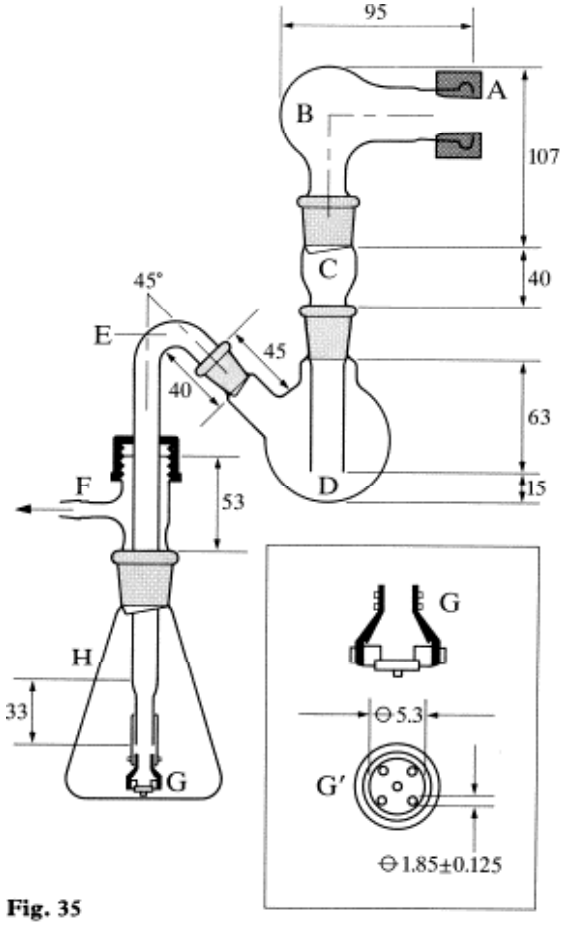
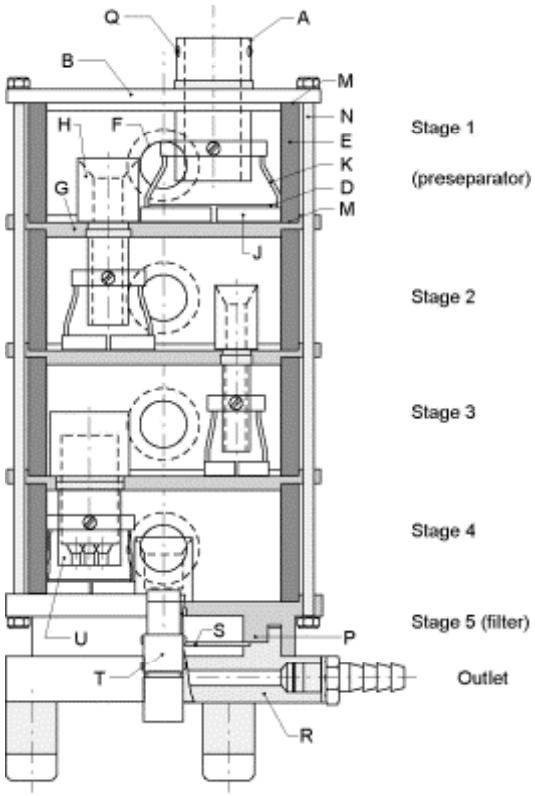
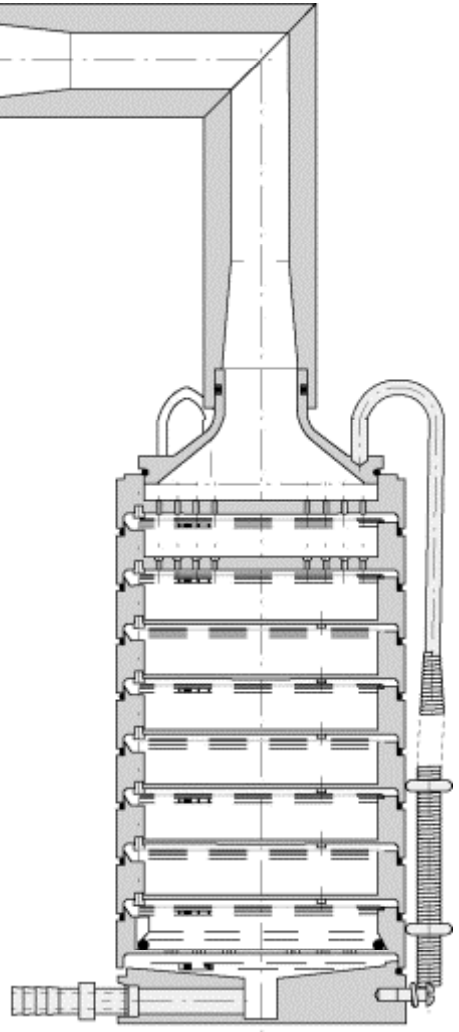


Fig. 35

Twin Stage impinger



Multi stage liquid impinger



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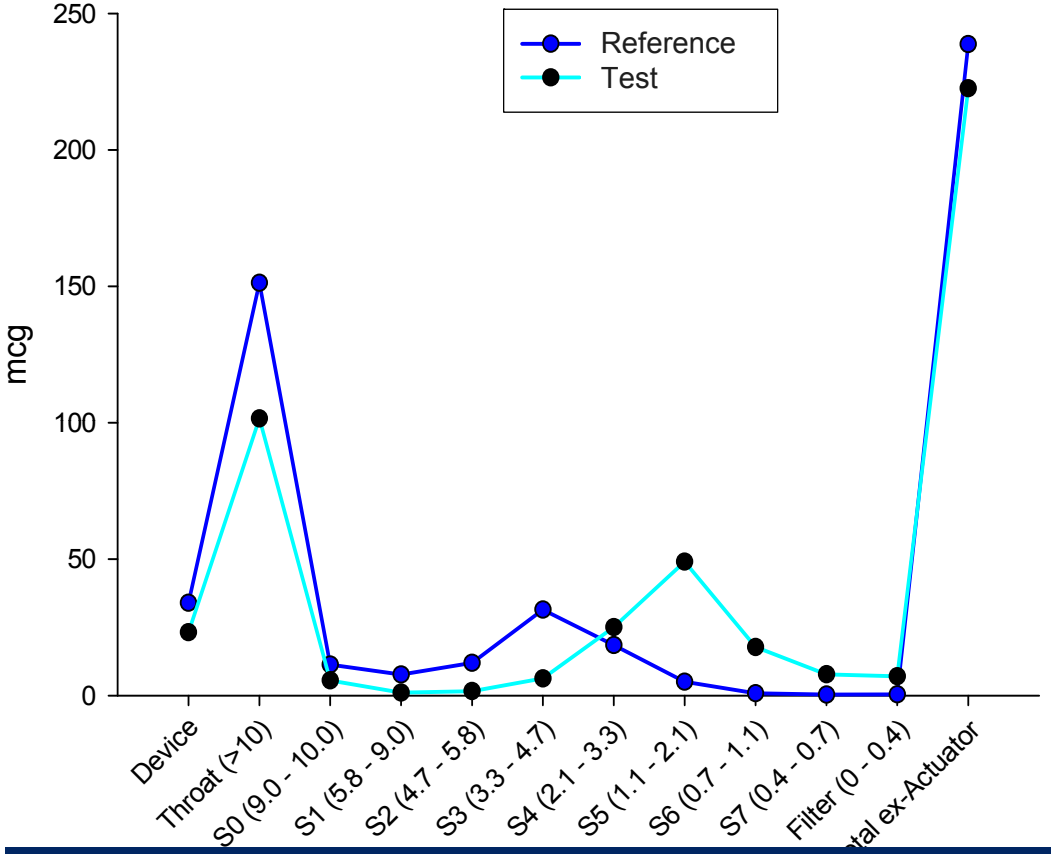
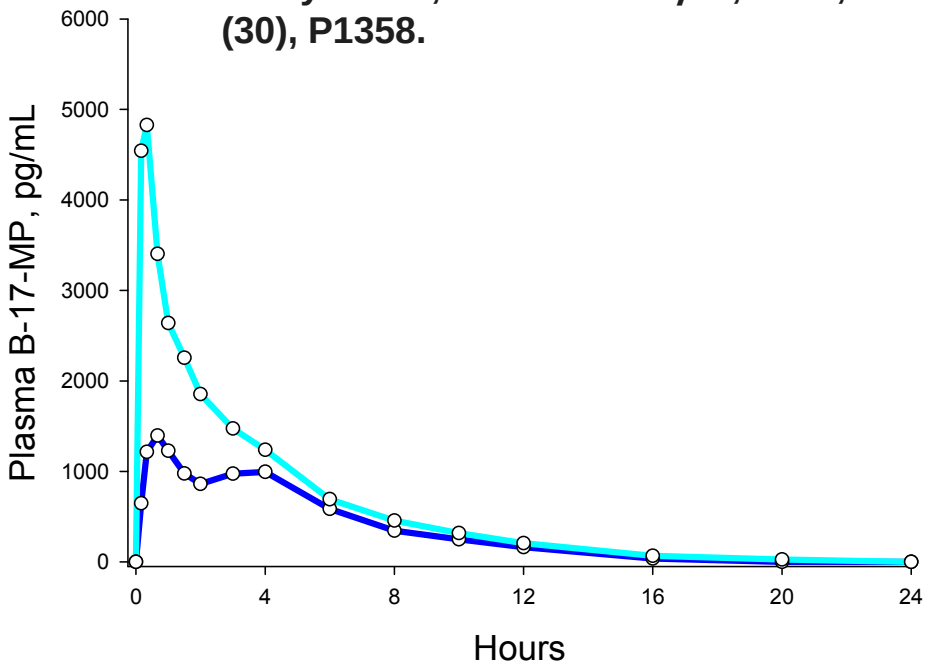
Outcome of in vitro inertial impaction and delivered dose assessment

Measurement does discriminate PK performance (P Daley Yates GSK)



Daley-Yates, et al *Eur Resp J*; 1999, 14 (30), P1358.



Ex-actuator: Test 223 / Ref 239: ratio = 0.93

FPM (Stage 3-5): Test 80 / Ref 55: ratio = 1.46

FPD (Stage 2-F): Test 114 / Ref 69: ratio = 1.65

FPM (Stage 4-F): Test 107 / Ref 25: ratio = 4.25

MMAD: Test = 1.3 µm Ref = 4.0 µm

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An Example of In-Vitro Demonstration of Bioequivalence

An example of successful *in vitro* only filing from Spain

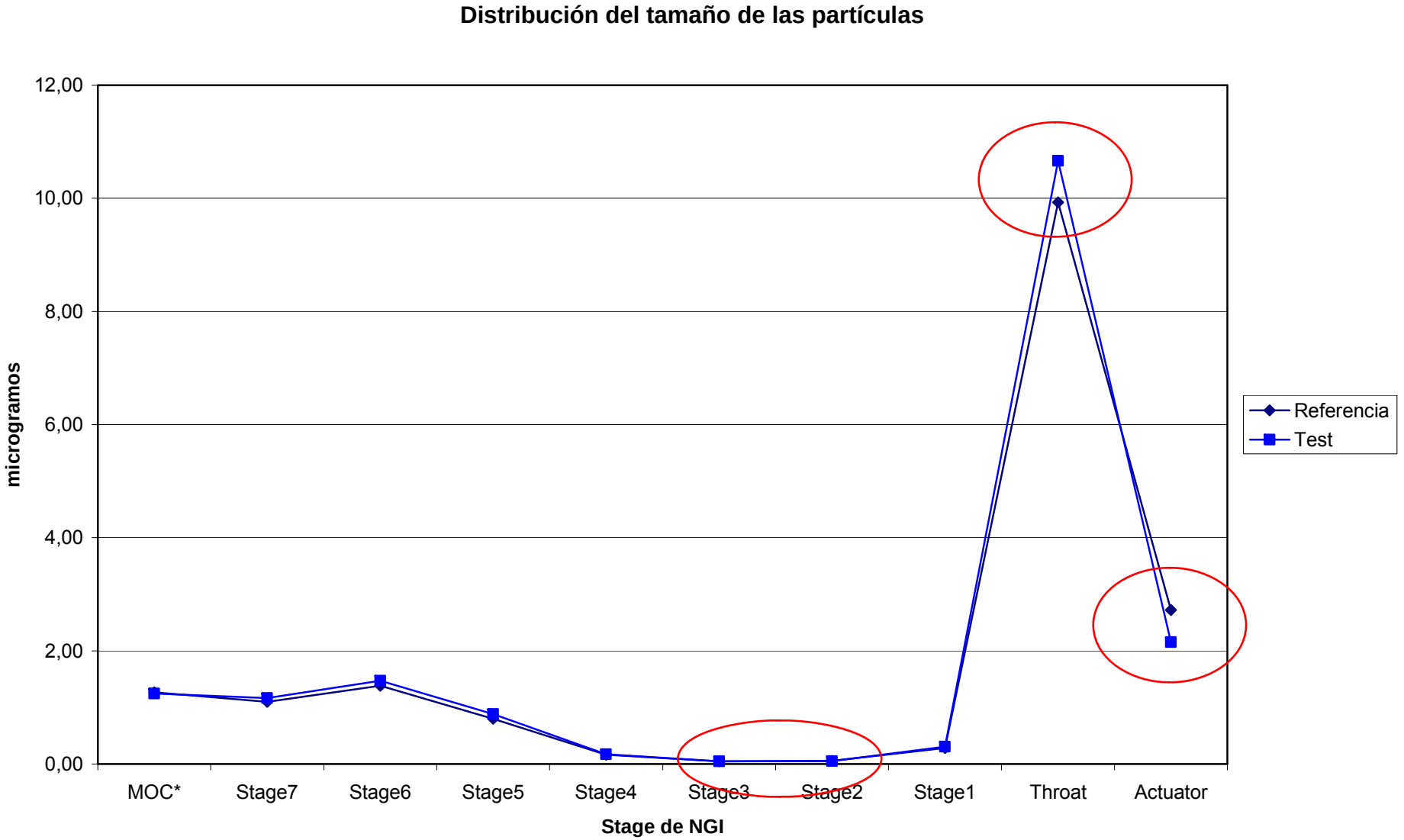
Data taken from Dr. Alfredo García – Arieta

- Ipratropium Bromide HFA pMDI
- Same composition Q_1 and Q_2
- Same valve
- Different canister size
- Different mouth adaptor

  Reference (Atrovent) vs. Generic

Aerodynamic Particle Size Distribution

Data taken from Dr. Alfredo García – Arieta @APS Inhalation 2015



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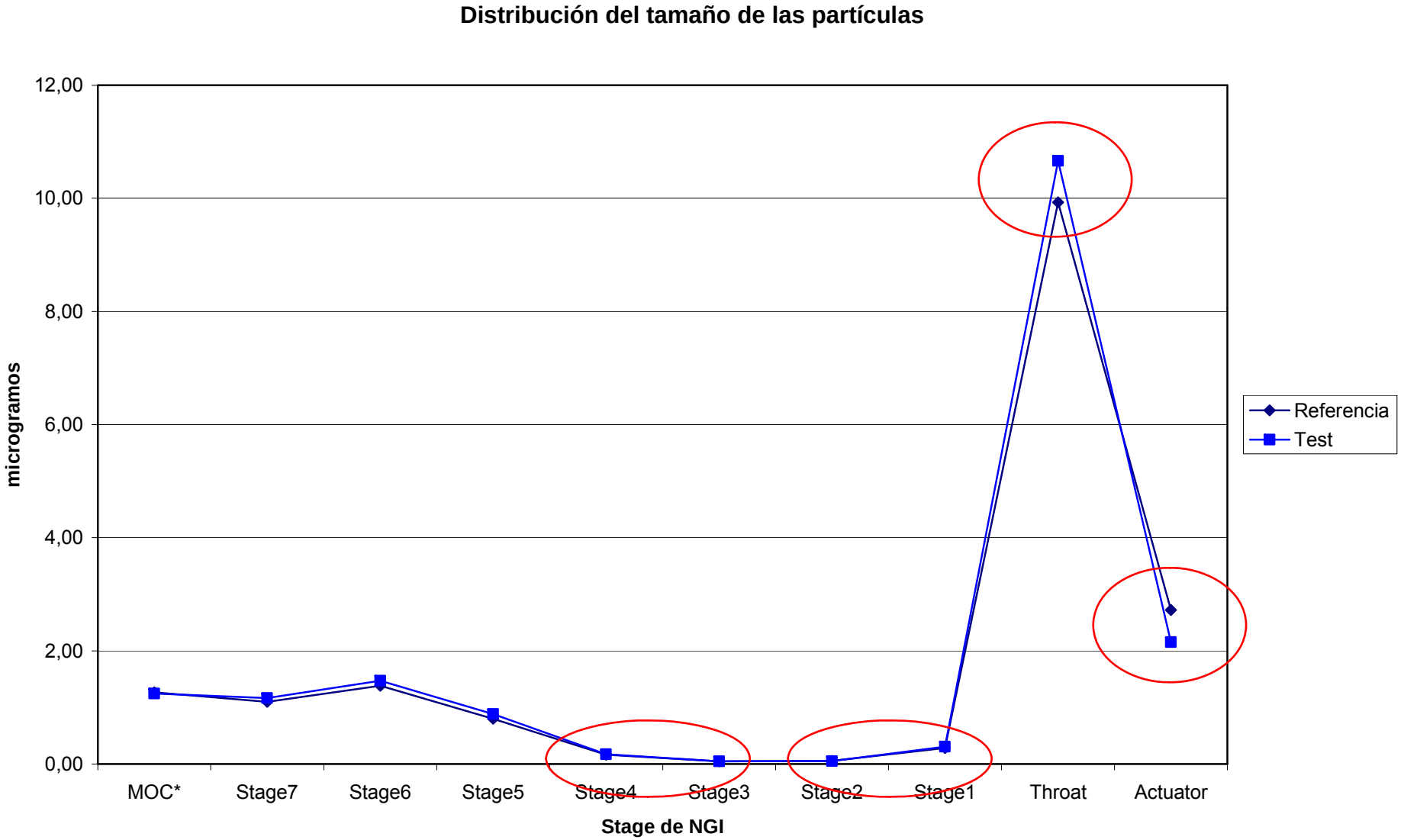
Aerodynamic Particle Size Distribution: No pooling of stage Data

Data taken from Dr. Alfredo García – Arieta

NGI	Size range (µm)	Test/Ref (%)	90% CI Limit	Acceptance (85-115%)
MOC	<0.541	97.8	101.2-94.4	Compliant
Stage 7	0.541-0.834	105.5	108.6-102.4	Compliant
Stage 6	0.834-1.357	106.0	108.9-103.3	Compliant
Stage 5	1.357-2.299	109.7	113.1-106.5	Compliant
Stage 4	2.999-3.988	105.7	112.7-99.2	Compliant
Stage 3	3.988-6.395	96.4	107.4-86.5	Compliant
Stage 2	6.395-11.719	87.3	97.0-78.6	Not compliant
Stage 1	>11.719	108.4	114.7-102.3	Compliant
Throat	-	107.4	109.3-105.4	Compliant
Actuator	-	80.4	85.4-75.7	Not compliant

Aerodynamic Particle Size Distribution

Data taken from Dr. Alfredo García – Arieta @APS Inhalation 2015



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Aerodynamic Particle Size Distribution

Stage Pooling – the rationale: Dr. Alfredo García – Arieta

- The comparison should be performed per impactor stage or justified group of stages.
  - Stage pooling decreases sensitivity
- At least 4 groups of stages are expected.
  - Based on MSLI – a legacy impinger with fewer stages.

In vitro characterization techniques for delivered dose and size

A range of devices exist for assessment of inhalable dose

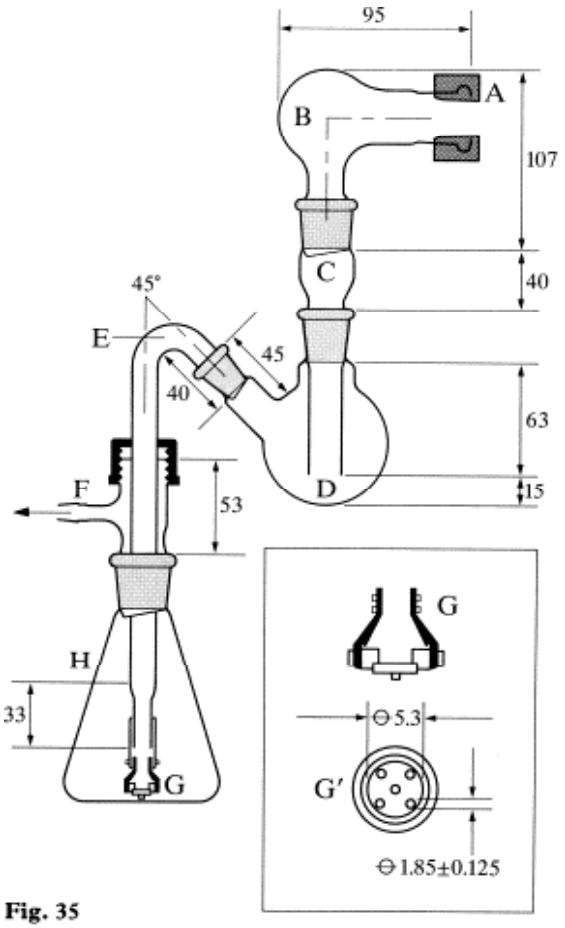
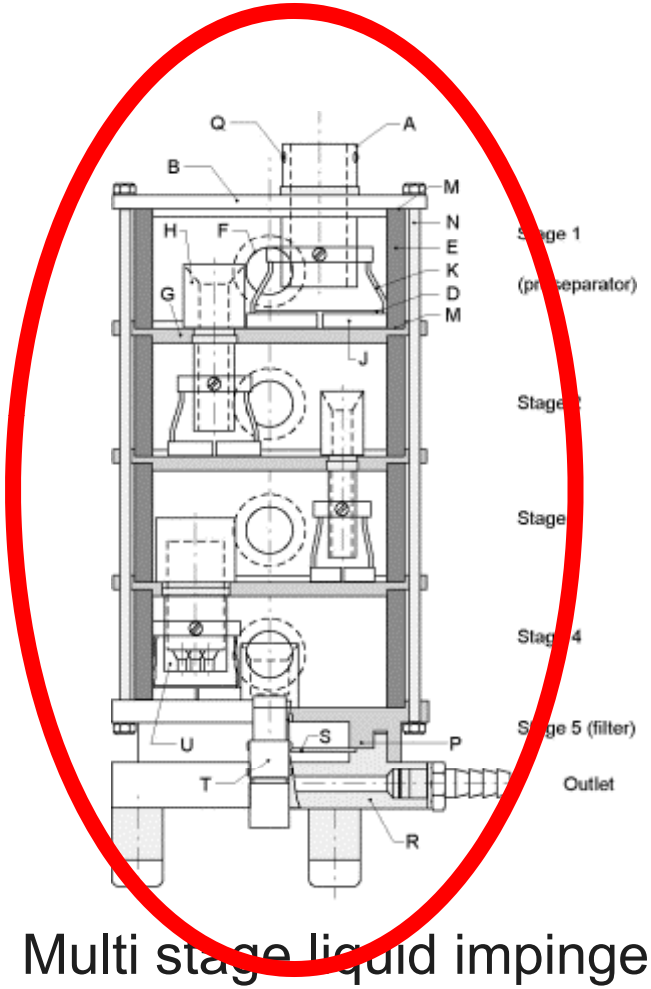
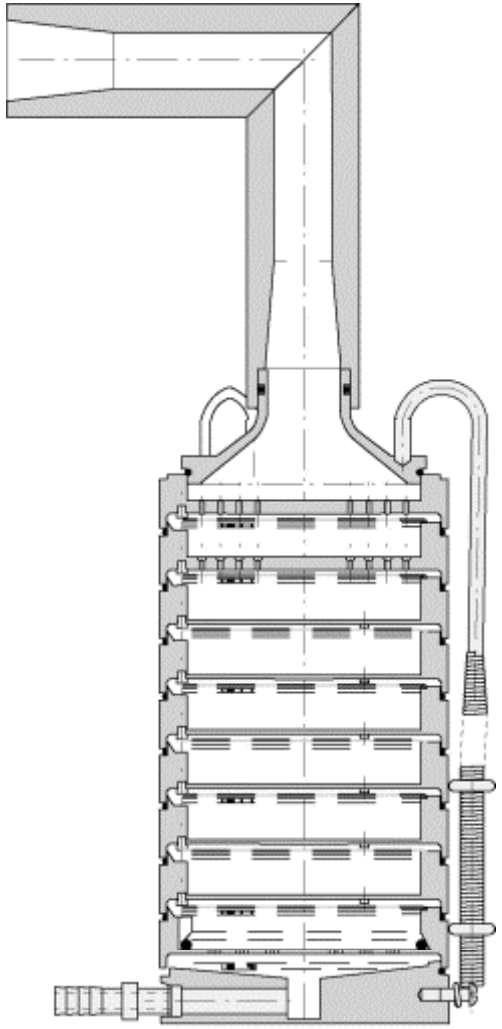


Fig. 35

Twin Stage impinger



Multi stage liquid impinger



Andersen Cascade Impactor

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Aerodynamic Particle Size Distribution

Stage Pooling – the rationale: Dr. Alfredo García – Arieta

- The comparison should be performed per impactor stage or justified group of stages.
  - Stage pooling decreases sensitivity
- At least 4 groups of stages are expected.
  - Based on MSLI – a legacy impinger with fewer stages.
- Issue – how to justify the stage groupings
  - Can impactor/impinger data ever reflect deposition sites in the lungs?
  - What is the size class that correlates to deposition (<3µm?)

Aerodynamic Particle Size Distribution: With pooling of stage data

Data taken from Dr. Alfredo García – Arieta

NGI	Size range (µm)	Test/Ref (%)	90% CI Limit	Acceptance (85-115%)
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Stage 3+4	2.999-3.988	105.5	113.2-98.3	Compliant
Stage 1+2	3.988-6.395	106.5	113.1-100.4	Compliant

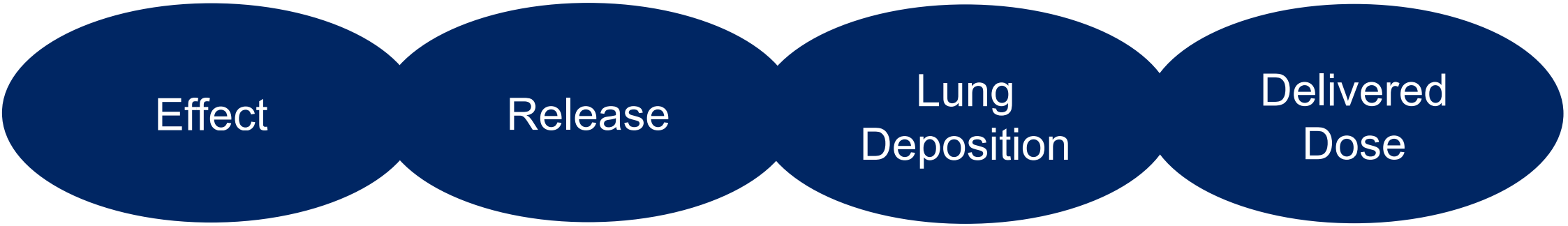
Sample selection issues in demonstrating equivalence

Sample size will really affect your chance of success (or failure)

- At least three consecutive batches of the test product and three batches of the reference product should be tested.
  - Which reference product batches do you chose?
  - More batches to reflect product variability
  - No real ethical issues for *in vitro* sample size
  - Number of canisters / batch not specified
  - Number of determinations / canister not specified
  - Actuations in different times of life cycle not specified

Outcome of stepwise demonstration of equivalence (B Ozsogut)

Understanding the scope for *in vitro* equivalency comparisons

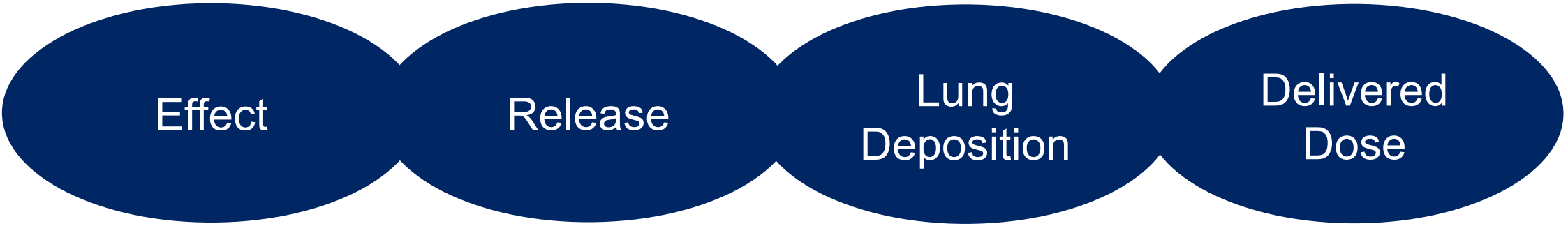


BEING GENERIC MEANS BEING SIMILAR

Effect	Release	Lung Deposition	Delivered Dose
YES / PK We can measure drug levels in plasma w/wo charcoal **YES / PD** We can measure efficacy	**NOT YET** Promising techniques being validated	**YES** Cascade impactor measurements gives detail results on APSD	**YES** We can measure delivered dose precisely

Outcome of stepwise demonstration of equivalence (B Ozsogut)

Understanding failure with *in vitro* equivalency comparisons



CHALLENGE TO SHOWING EQUIVALENCE IS IN THE DETAIL

Effect	Release	Lung Deposition	Delivered Dose
PK Dosing manoeuvre is the key **Statistics** should count reference variation **PD** not sensitive	**No** pharmacopeial method available **Needs to be validated** against in-vitro & in-vivo data	Analytical Method Variation Reference Product Variation	Analytical Method Variation Reference Product Variation

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Human Factors Issues for Inhaled Product Performance and Designing User-Focussed Testing Approaches

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Pharmaceutical properties and the need for a clinical programme

Examining the *in vitro* testing opportunities

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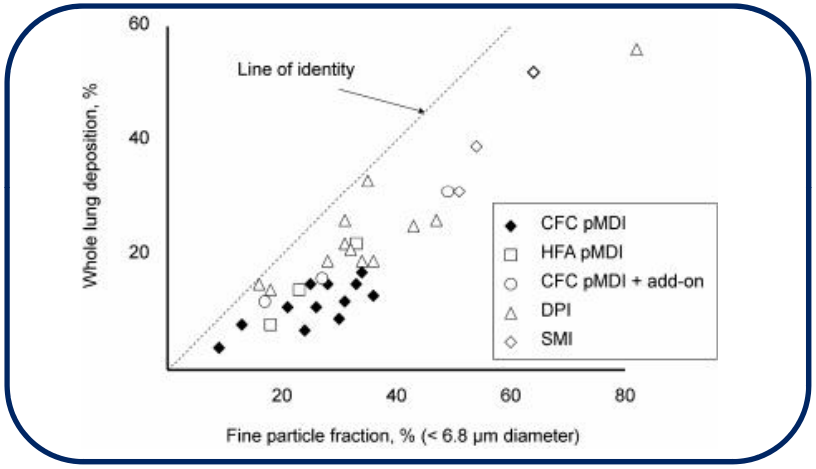
In vitro/in vivo comparisons in pulmonary drug delivery

But key doubts remain over in vitro-in vivo correlations

"few published data that relate APSD to the clinical response of inhaled drugs in an unambiguous way"

Newman and Chan; J Aerosol Med. 21 (2008) 77-84



In vitro FPD may over-estimate WLD

In vitro/in vivo comparisons in pulmonary drug delivery

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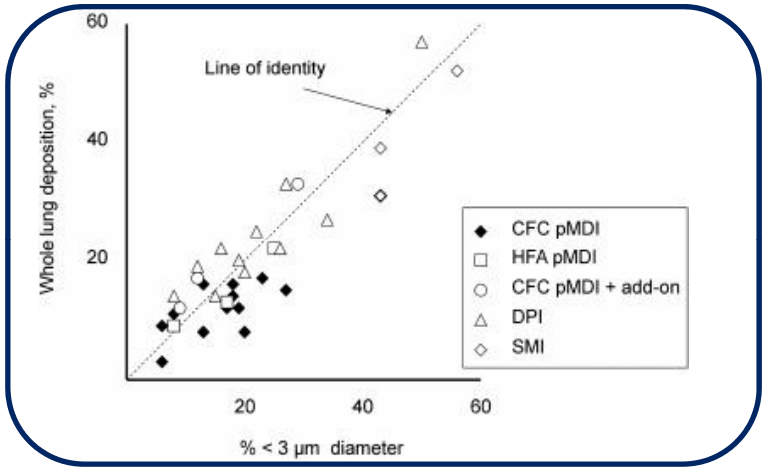


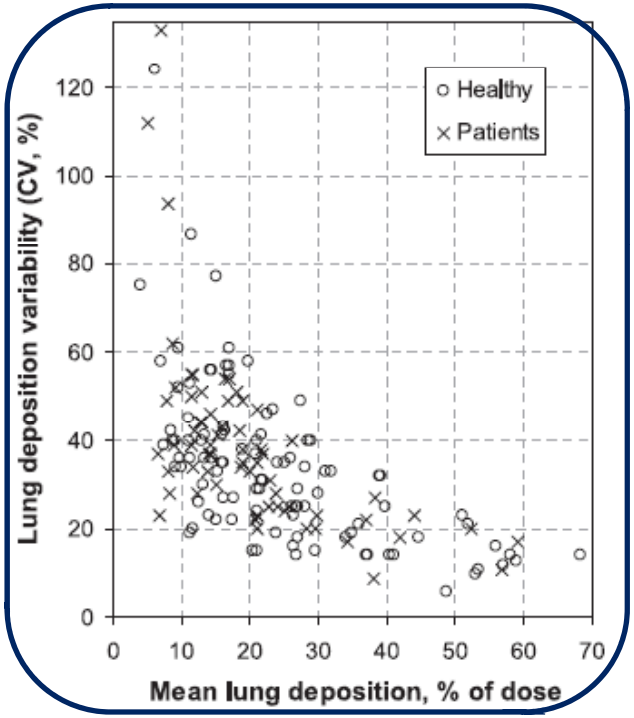
In vitro FPD may over-estimate WLD

- Better correlation for extra-fine particle dose (< 3 µm)
- Slow moving aerosol products achieve over-lap

In vitro/in vivo comparisons in pulmonary drug delivery

But key doubts remain over in vitro-in vivo correlations

"few published data that relate APSD to the clinical response of inhaled drugs in an unambiguous way"



Borgstrom et al; J Aerosol Med. 19 (2006) 473-483

In vitro FPD may over-estimate WLD

- Better correlation for extra-fine particle dose (< 3 μm)
- Slow moving aerosol products achieve over-lap
- Simulating throat anatomy at inlet may offer better correlation
- Clear link between inter-patient variability in WLD and the extent of oropharyngeal deposition

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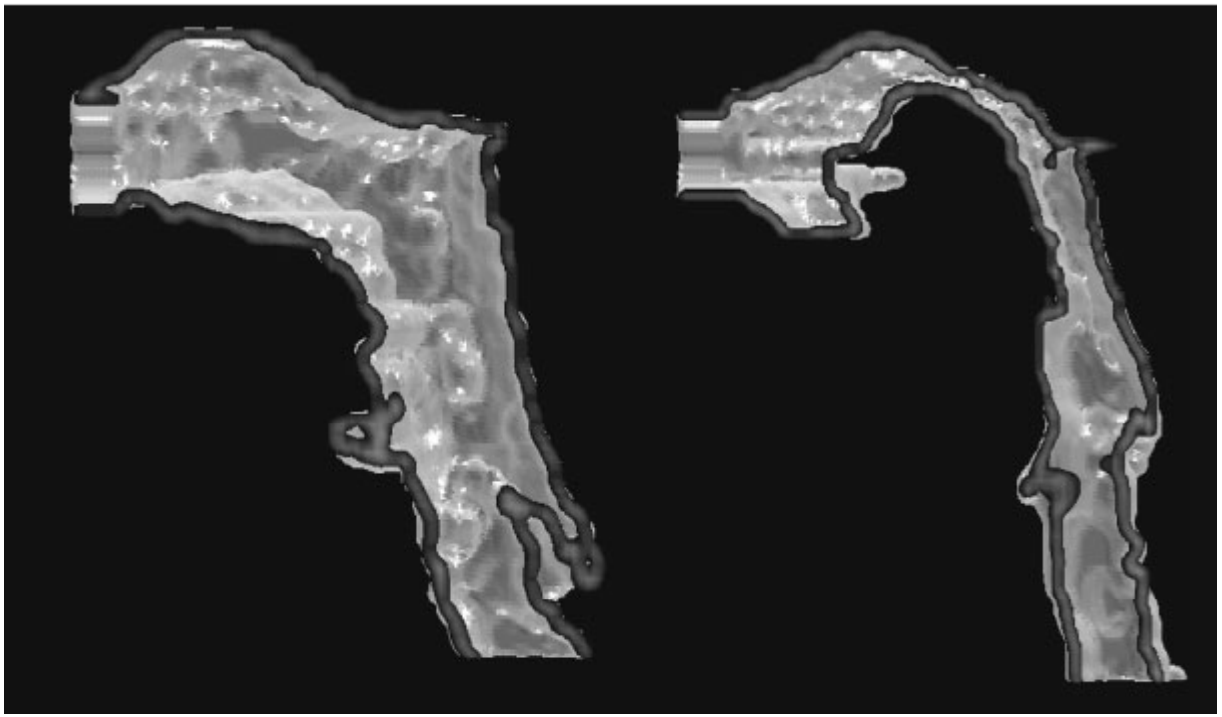
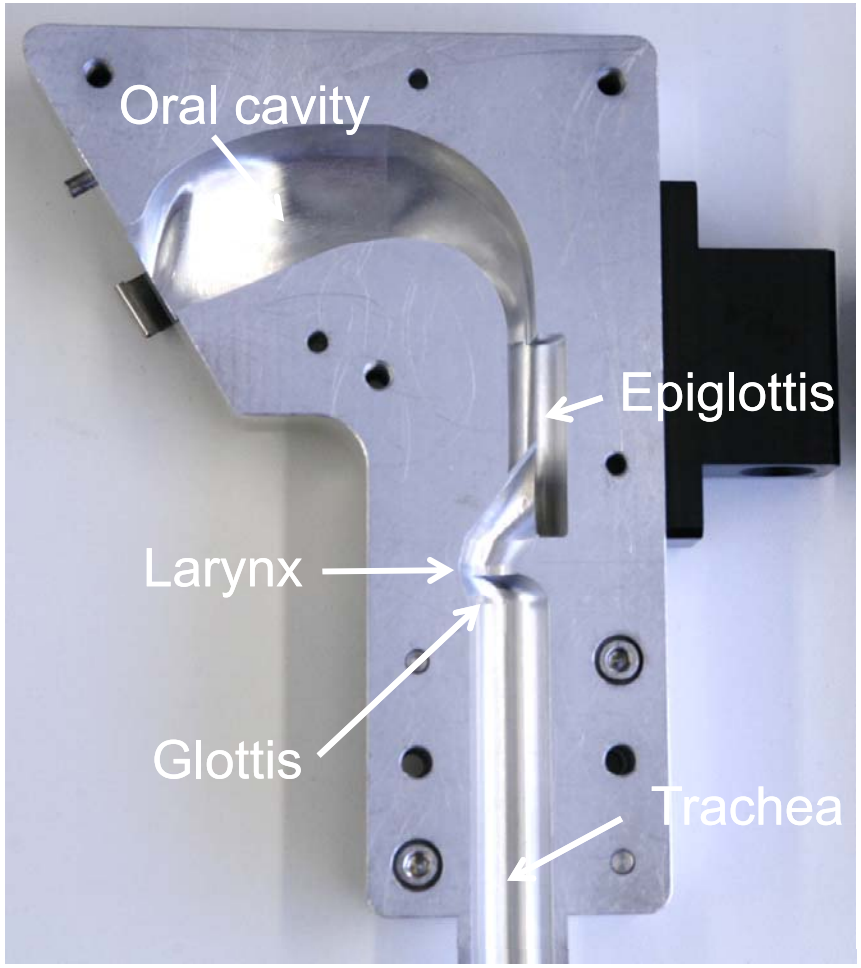
Moving toward patient-focussed *in vitro* testing approaches

Improving modelling of the throat for *in vitro* data

Low resistance device High resistance device



Ehtezazi et al. J. Pharm. Sci. (2005) 94: 1418–1426



Finlay, WH Experiments in Fluids 2004, 37: 673-689

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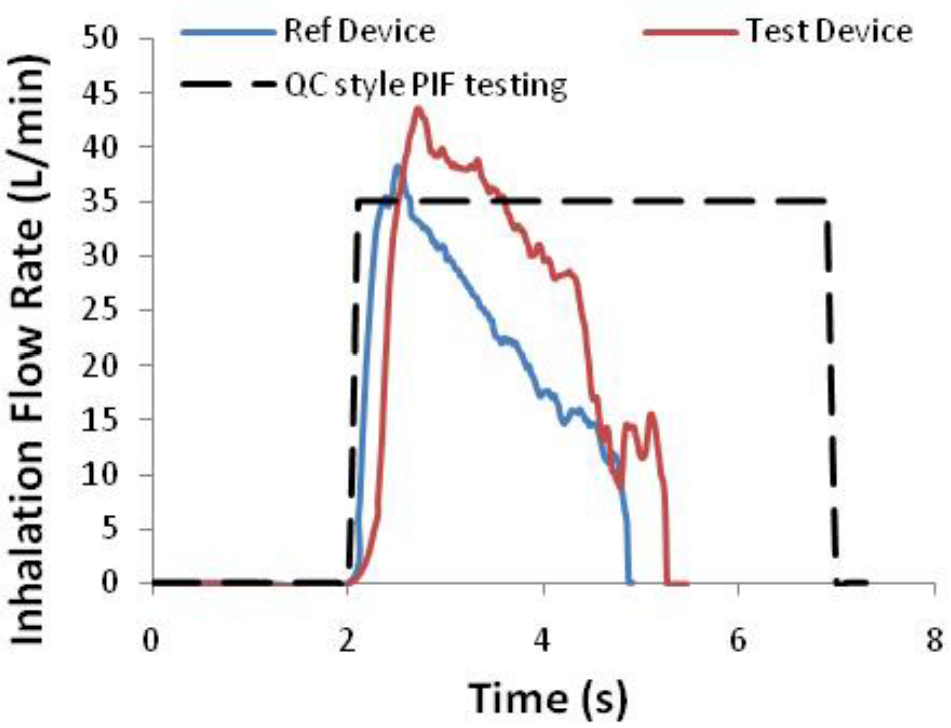
Moving toward patient-focussed *in vitro* testing approaches

Can ‘inhalation’ maneuver be made more physiologically accurate?

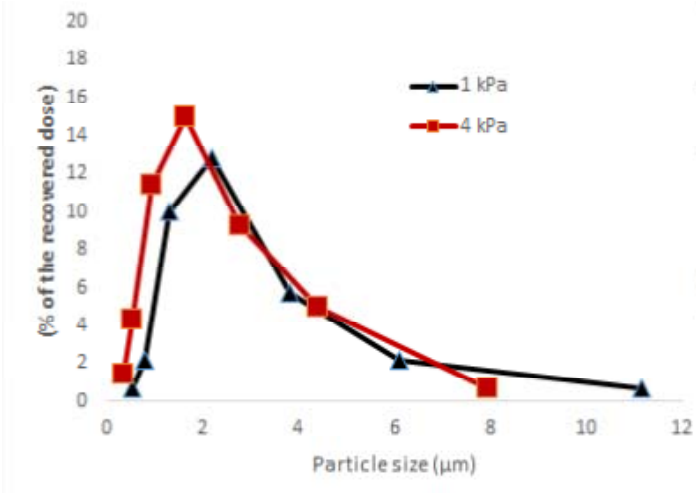


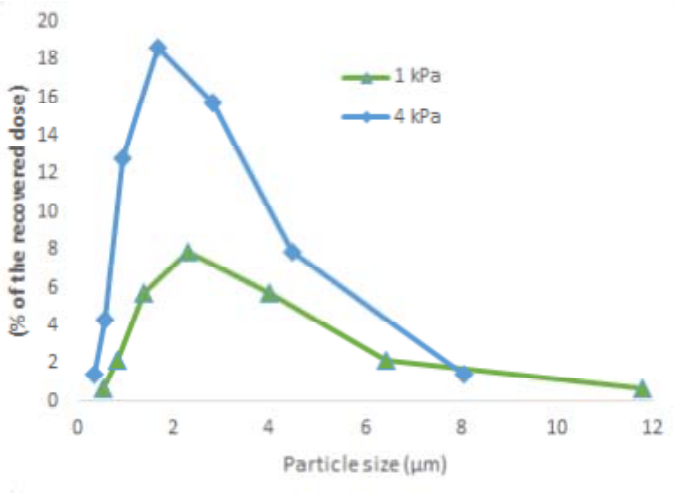
- Not every patient in our volunteer or clinical study will inhale at the same/optimal flow rate & variability is highest for high resistance devices
- Should we test at the actual peak flow? Should we use real breath profiles?

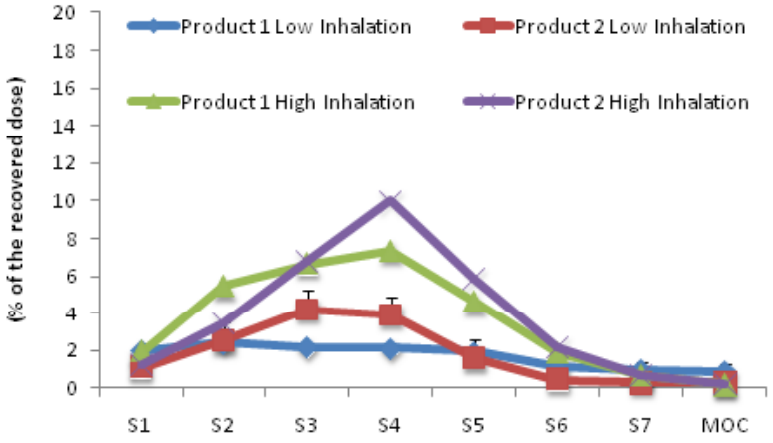
When is a DPI a generic or an equivalent branded product?

DPIs that differ in resistance, handling and inhalation volume

2 Products X 2 profiles







- QC Aerosolization Volume: 4 L, lasting 2.7 s or 4.0 s

- Simulated inhalations:
  - Product 1: 1.1 & 2.6 L, lasting 2.7 & 2.1 s
  - Product 2: 1.4 & 2.9 L, lasting 3.0 & 2.0 s

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Murnane et al. Unpublished Data (2014)
APSGB-Aerosol Society Symposium.

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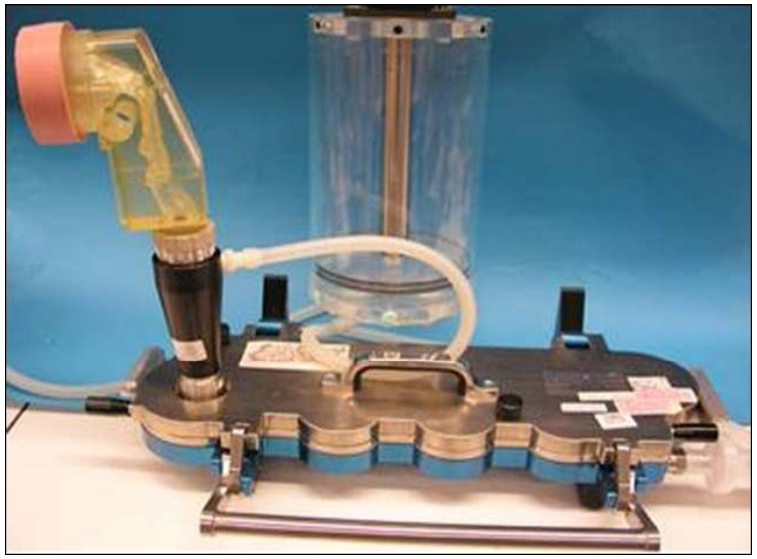
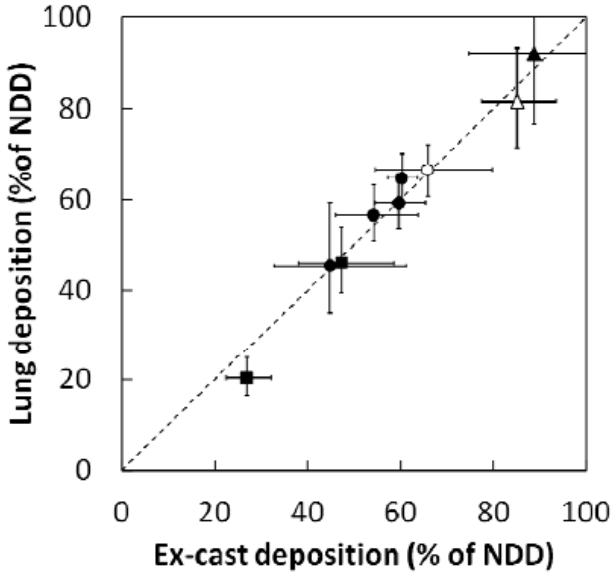
Employing clinically-relevant models improves deposition prediction

But does not guarantee in vitro in vivo correlation for PK data





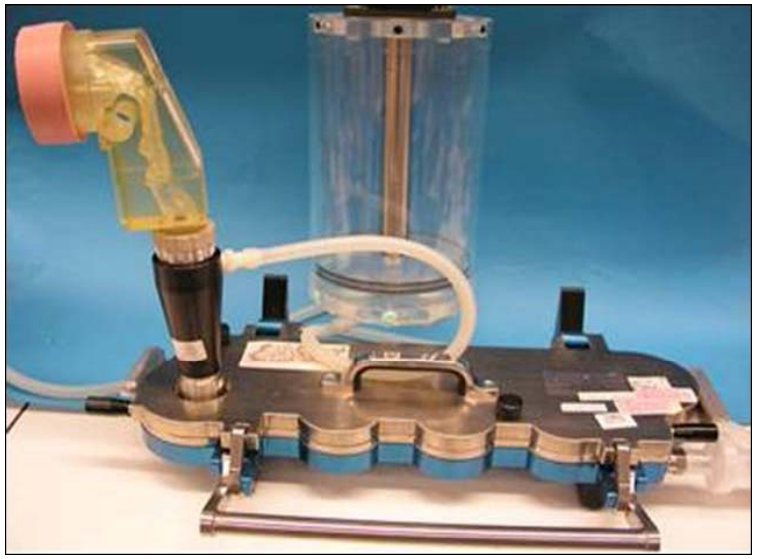
PK outcome
??????

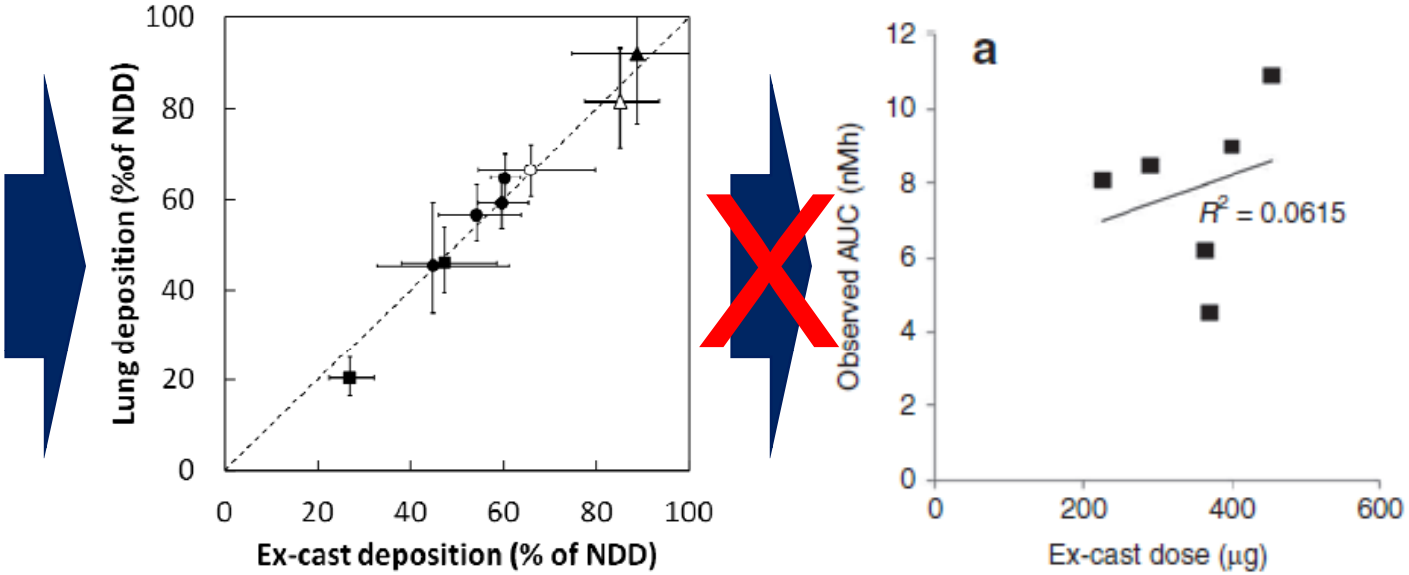
Olsson et al. J. Aerosol Med. (2013) 26: 355-369; Olsson et al. (2013) DDL 25; Backman & Olsson, IPAC-RS Orlando Meeting (2014); Backman et al. Clin. Pharmacol. Ther. (2014) 95: 509-520

Patient-focussed testing offers a robust approach to compare between devices

Employing clinically-relevant models improves deposition prediction

But does not guarantee in vitro in vivo correlation for PK data





Olsson et al. J. Aerosol Med. (2013) 26: 355-369; Olsson et al. (2013) DDL 25; Backman & Olsson, IPAC-RS Orlando Meeting (2014); Backman et al. Clin. Pharmacol. Ther. (2014) 95: 509-520

Patient-focussed testing offers a robust approach to compare between devices

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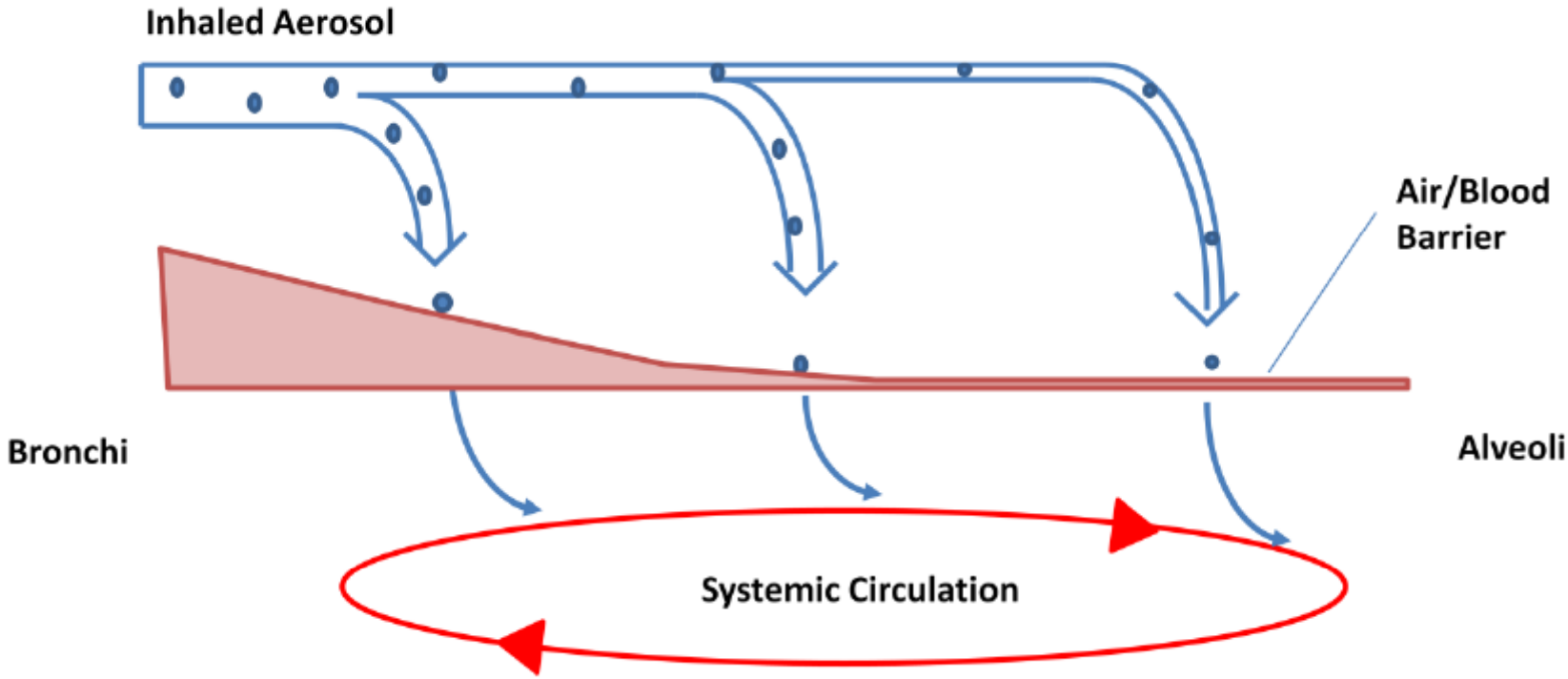
Key factors determining drug delivery to lung sites: It's not just size!

The deposition site, release and absorption are inter-linked



Per Gerde, Karolinska Institutet, Sweden. DDL 2014

Questions raised:

1. Density of deposited material on the test surface
2. Deposition pattern affecting the deposited mass

Further questions:

1. Properties dictating deposition
2. Properties dictating release
3. Properties dictating transport & absorption away from target site

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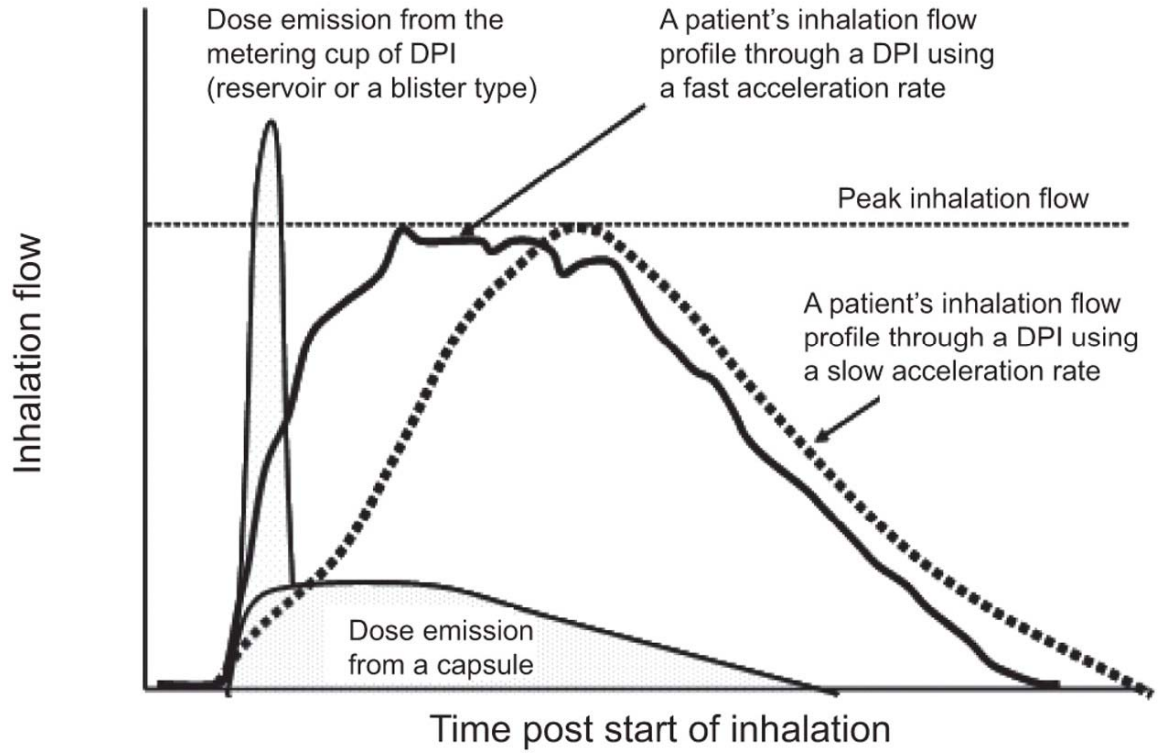
Physiologically-based assessment of inhaled dose

The inhalation profile and device design affect aerosol bolus profile

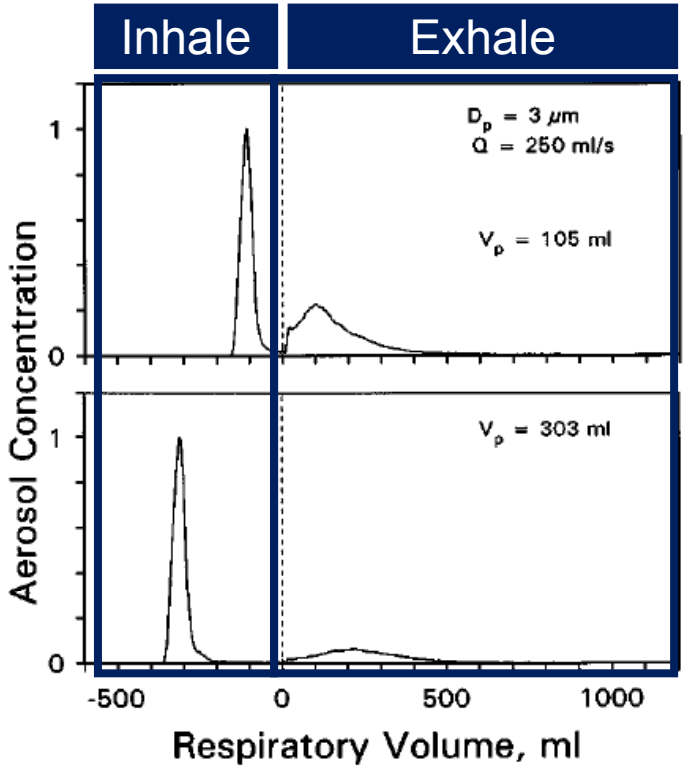


Aerosol emission rate depends on device design and total dose. Even for patients with identical PIFs, drug may enter different lung volumes

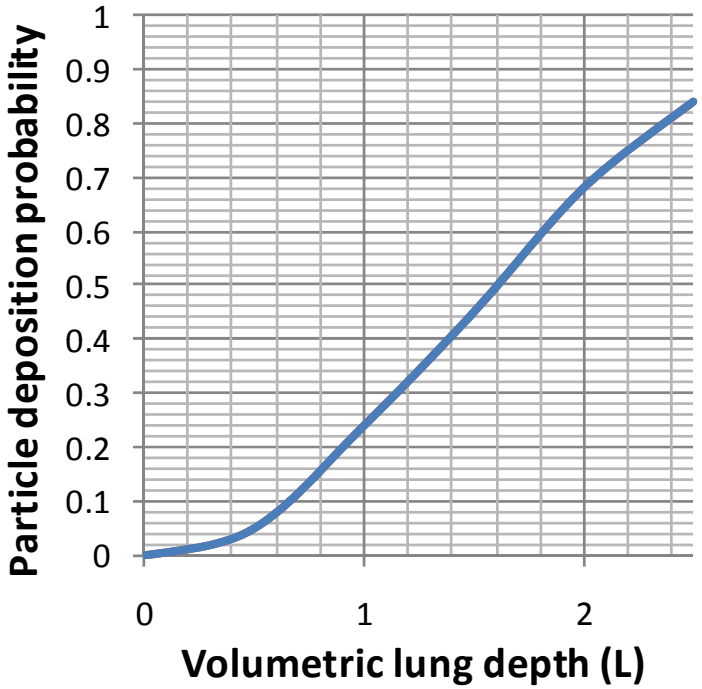
B.L. Laube et al. Eur Respir J 2011;37:1308-1417

Physiologically-based assessment of inhaled dose

Deposition of aerosol is determined by the volume of inhalation



Kim et al. J Appl. Physiol. 1996, 81: 2203-2213



Data modelled from Brand et al. J. Aerosol Med. (1999) 12: 275-284.

Aerosols particles contained in volume elements penetrate to different depths
Particle deposition increases with its depth (V) of penetration

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Our current work in this area

- Engineering of generic devices to better control the emission point of the aerosol in the inhalation profile
- Can inhalation profile modelling be employed to match volunteers for T & R products?
- A 5-year study is beginning to develop in vitro deposition methods that better predict regional deposition in the lung, not just whole lung deposition.

Patient-focused testing of physical device handling issues

Physical barriers to metered dose inhaler use

Device handling and pMDI actuation

Most reports into the use of pMDIs in the elderly focus on the cognitive ability of individuals to learn and co-ordinate actuation with inhalation [1]

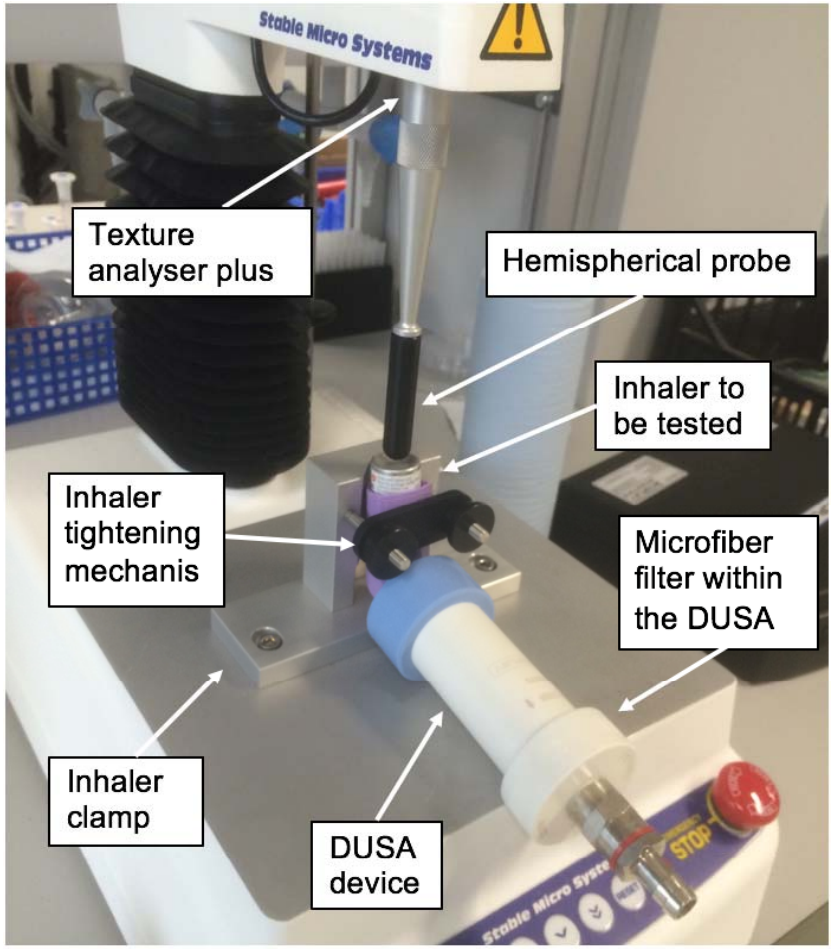
A few as 29 % of older patients possessed sufficient strength to fire all marketed pMDIs[2]

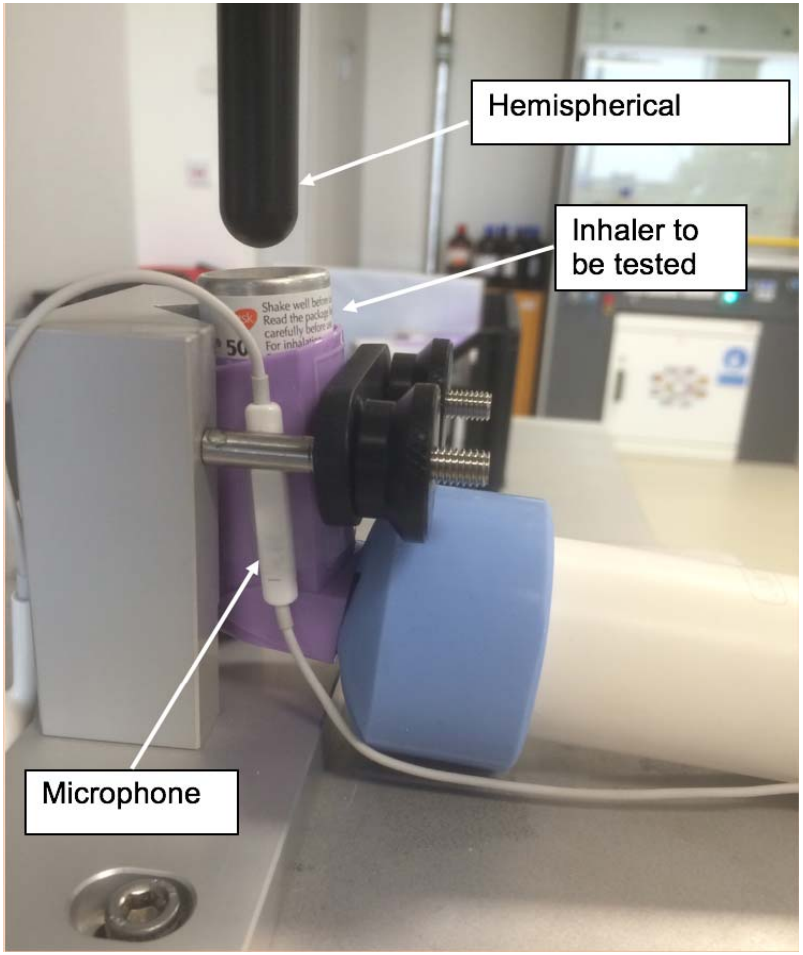
As many as 36 % of older patients unable to actuate any pMDI[2]

[1]Rau, 2006, Respiratory Care 51(2)
[2]Armitage and Williams 1988, Age and Ageing 17(4)

Physical barriers to metered dose inhaler use

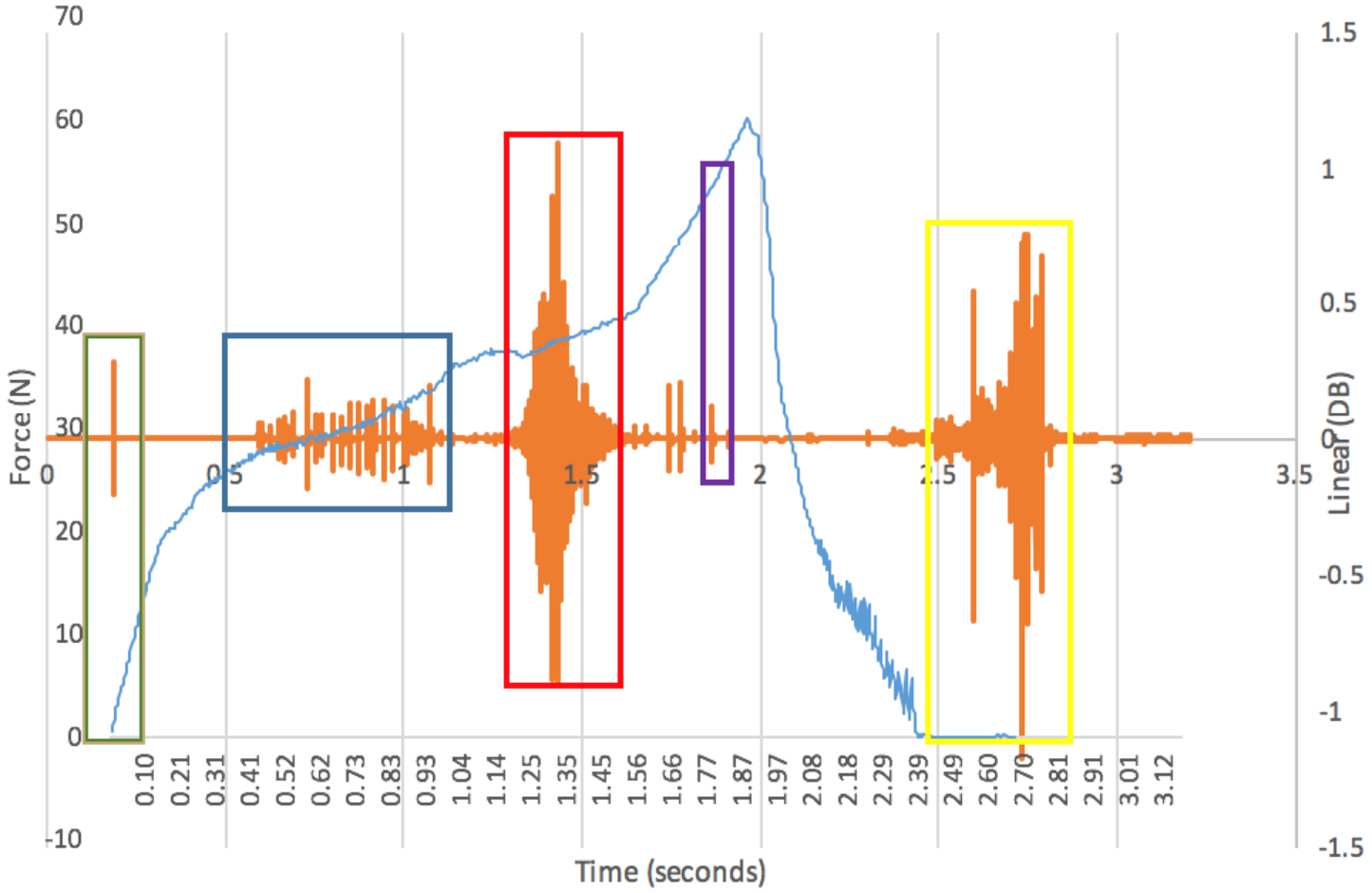
Assessing the mechanical actuation process for pMDIs





Physical barriers to metered dose inhaler use

Identifying mechanical events during actuation



Key:

= Point on canister contact

= Spring depression

= Actuation (valve opening)

= End of spring depression

= Spring uprising

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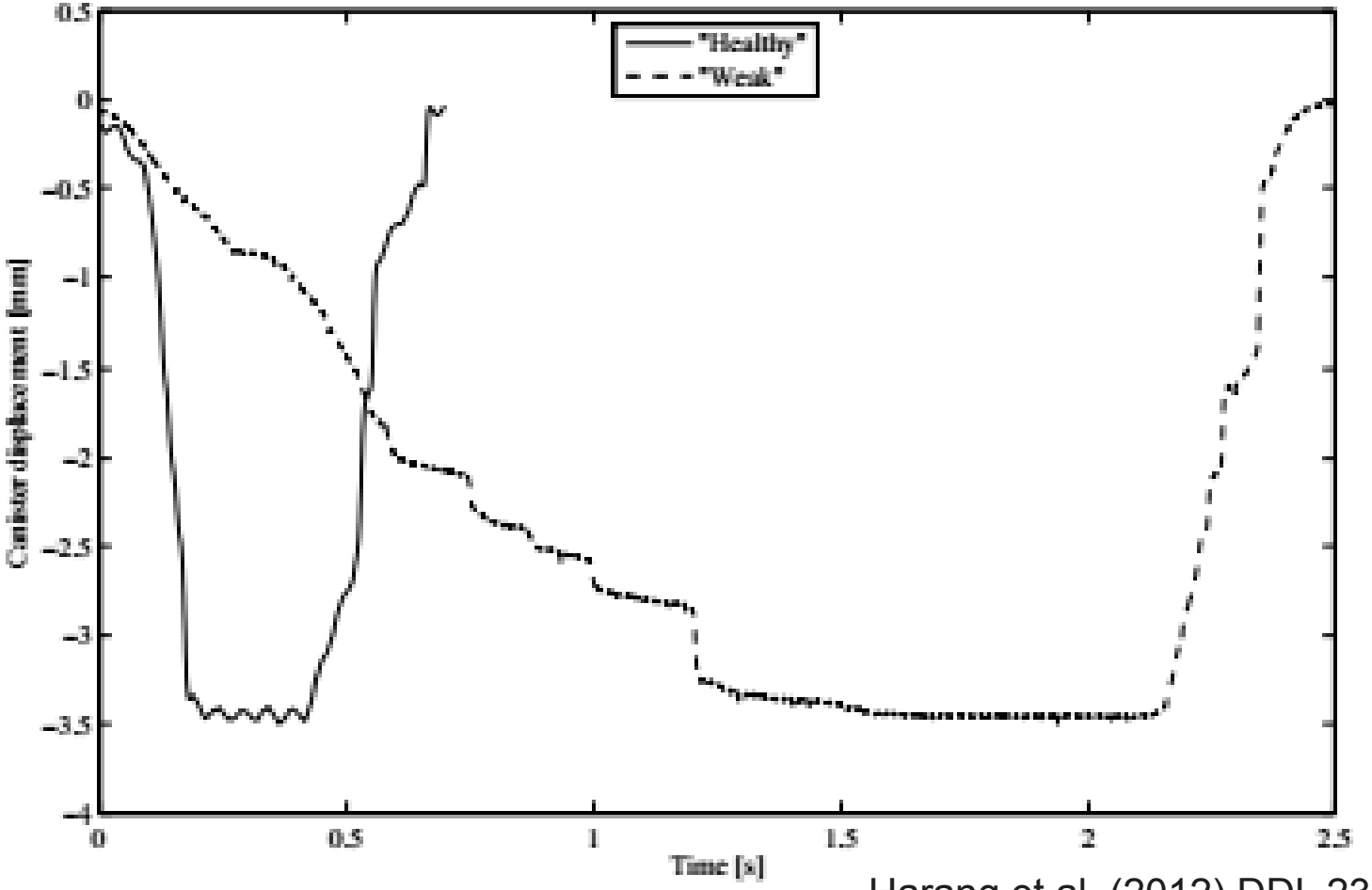
Physical barriers to metered dose inhaler use

Force displacement using linear variable displacement transducer



Harang et al. (2012) DDL 23 Conference;
Harang (2013) KCL PhD thesis.

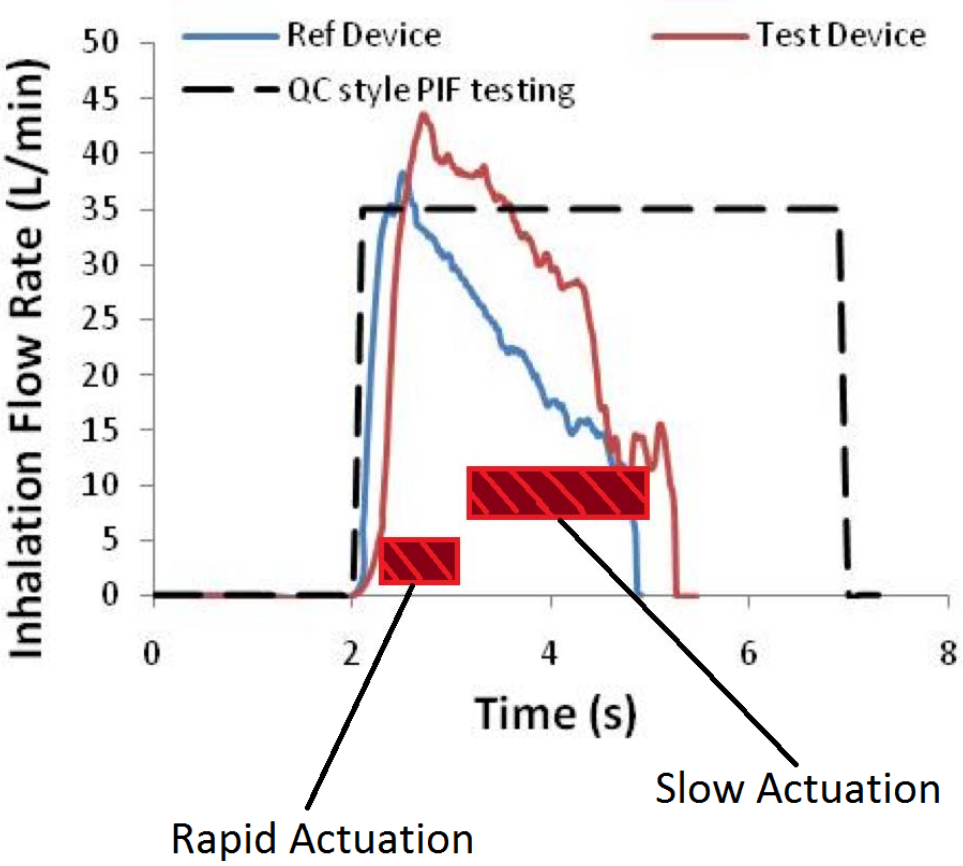
Physical barriers to metered dose inhaler use

Time and duration of actuation event

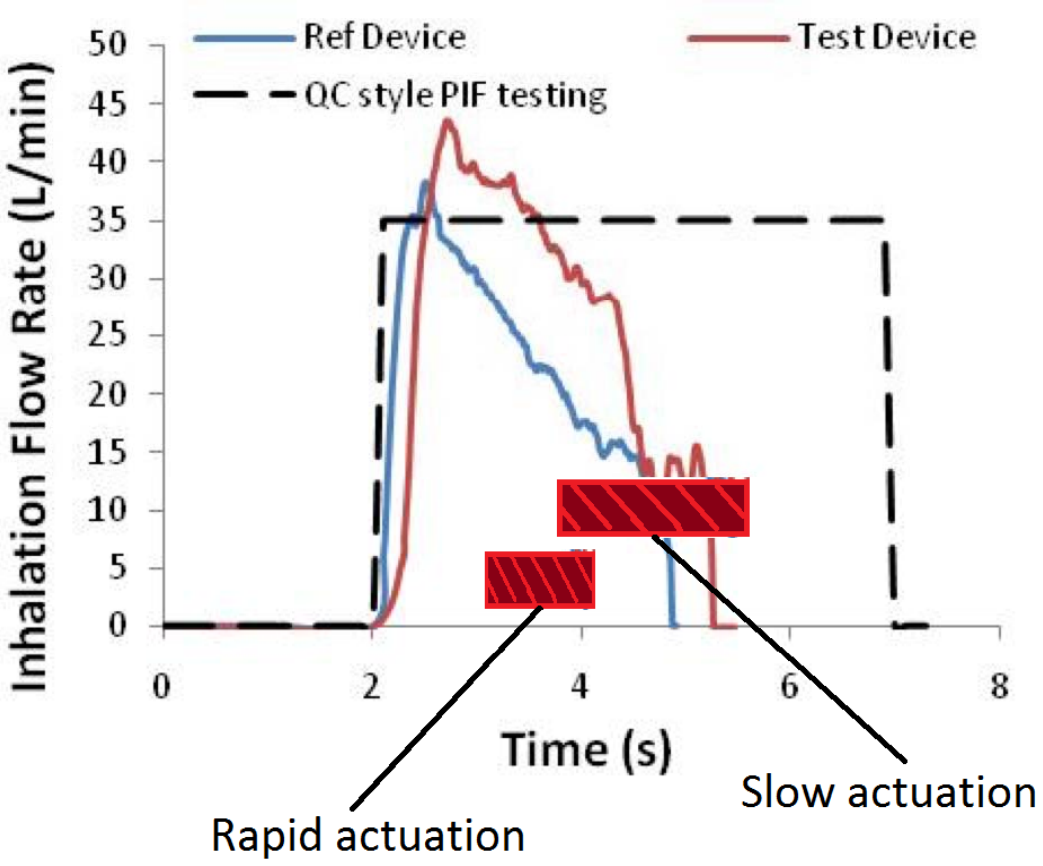
Inhaler	Time to actuation (seconds)	Duration of actuation (seconds)
Ventolin Rapid	0.143	0.121
Ventolin Slow	1.226	0.303
Clenil Rapid	0.135	0.188
Clenil Slow	2.905	0.319
QVAR Rapid	0.594	0.197
QVAR Slow	2.853	0.313

Poor coordination may not an issue of cognition for patients with impaired manual dexterity

Good coordination



Poor coordination



Our current work in this area

- Human factors study, funded by the USA Food and Drug administration to investigate how device mechanical features may impact on the perception of difference between inhalation products.

Thank you for your attention!

In vitro equivalence testing
APS Inhalation Bioequivalence Workshop speakers, Garcia-Arieta, Ozsogut, Daley-Yates, Ozsogut, Price & Rogueda, and deposition data Dr Farnaz Esmaeili (KCL)

MDI Device Handling Study
Akshay Patel (University of Hertfordshire)

EPSRC for funding
D Murnane and ongoing work EP/N025075/1
Other associated funding:
Hertfordshire Local Enterprise Partnership & Dept for BEIS
Ministry of Housing, Community and Local Government

EPSRC
Engineering and Physical Sciences Research Council

Hertfordshire
Local Enterprise Partnership
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European Union
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