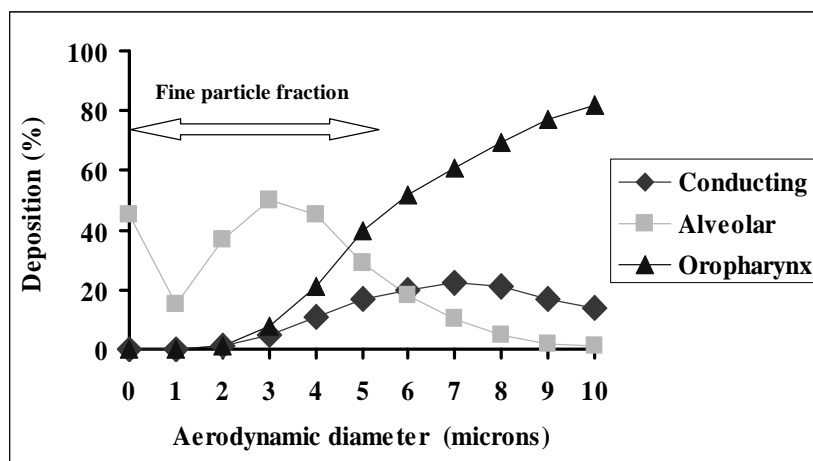


## CLINICAL RELEVANCE OF IN VITRO PARTICLE SIZING DATA

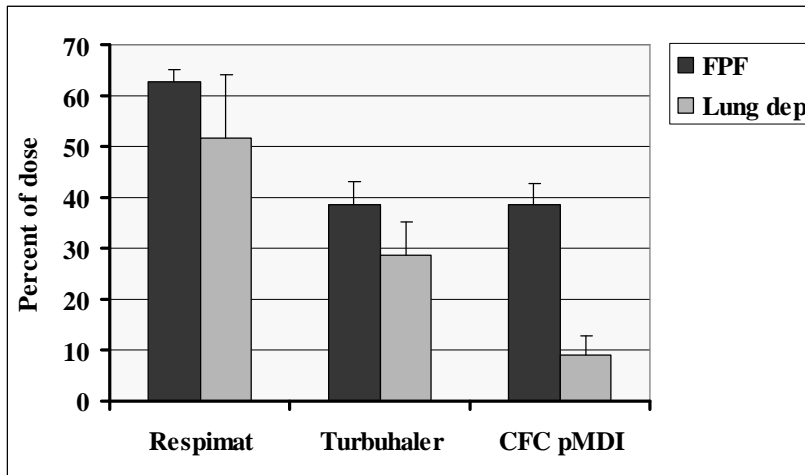
Steve Newman, PhD  
Nottingham, UK  
November 2006

### EFFECT OF PARTICLE SIZE ON AEROSOL DEPOSITION

From Heyder et al 1996



**MEAN (SD) FINE PARTICLE FRACTION (FPF)  
vs WHOLE LUNG DEPOSITION FROM THREE INHALERS**  
From Pitcairn et al 2005



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**CROMOLYN SODIUM DEPOSITION AND CLINICAL  
RESPONSE IN 8 ASTHMATIC PATIENTS**  
Mean and SD data from Laube et al 1998

	<u>Slow Inhalation</u>	<u>Fast Inhalation</u>	<u>P</u>
<b>Whole lung dep. (%)</b>	<b>11.8 (3.5)</b>	<b>8.6 (3.9)</b>	<b>&lt;0.05</b>
<b>Inner/outer lung ratio</b>	<b>3.1 (2.2)</b>	<b>5.3 (2.3)</b>	<b>&lt;0.05</b>
<b>Lung distribution skew</b>	<b>2.4 (0.4)</b>	<b>3.0 (0.4)</b>	<b>&lt;0.05</b>
<b>Fall in FEV<sub>1</sub> (after antigen challenge)</b>	<b>5.4 (4.2)</b>	<b>12.6 (11.0)</b>	<b>&lt;0.05</b>

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**PARTICLE SIZE / DEPOSITION / CLINICAL EFFECTS  
OF PHARMACEUTICAL AEROSOLS**

**AERODYNAMIC  
PARTICLE  
SIZE  
DISTRIBUTION**

**AEROSOL  
DEPOSITION**

**CLINICAL  
EFFECTS**

**PARTICLE SIZE / DEPOSITION / CLINICAL EFFECTS  
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**AERODYNAMIC  
PARTICLE  
SIZE  
DISTRIBUTION**

**AEROSOL  
DEPOSITION**

**CLINICAL  
EFFECTS**

**?**

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**AERODYNAMIC PARTICLE SIZE vs CLINICAL EFFECT**

- § **What is the clinical significance of change or variability in APSD from an inhaler device?**
- § **What change in APSD is clinically relevant?**
- § **Four-fold change in inhaled steroid dose may be needed to detect a difference in response (Barnes et al 1998)**
- § **Widespread belief that for a drug with a wide therapeutic window, APSD can vary considerably without a clinically significant change in response**  
**ØDo published literature studies support this belief?**

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## AERODYNAMIC PARTICLE SIZE vs CLINICAL EFFECT

- § How does the APSD / clinical effect relationship vary between
  - Ø Different drug categories?
  - Ø Asthma vs. COPD?
  - Ø Different degrees of airflow obstruction?
- § What is the relevance of APSD data under the Quality by Design paradigm?
- § Would a better understanding of in vitro / in vivo correlations enable more clinically meaningful APSD specifications to be set?

## DATA REVIEW

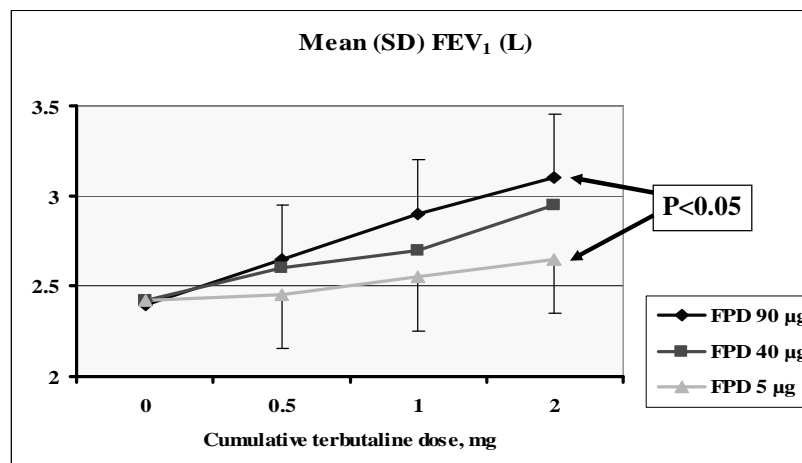
- § A review of published data linking APSD to clinical effect of inhaled drugs
  - Ø Instigated by IPAC-RS Cascade Impactor Working Group
  - Ø Joint review by Steve Newman and Kim Chan (University of Sydney)
- § Primary data set:
  - Ø Studies comparing two or more aerosols of different sizes from the same or similar pMDI or DPI
- § Secondary data set:
  - Ø Comparison of nebulizers with different APSDs
  - Ø Other pMDI or DPI data: e.g. CFC vs HFA pMDIs
  - Ø Monodisperse pharmaceutical aerosol studies

## PRIMARY DATA SET

- § Few published pMDI or DPI studies have been conducted to examine APSD / response relationship
- § Five clinical studies in patients with asthma:
  - Ø Bronchodilators 4; cromolyn sodium 1
  - Ø pMDI 4; Turbuhaler DPI 1
- § Single-dose and cumulative-dose designs
- § All studies published between 1982 and 1991 in a range of medical and pharmaceutical journals

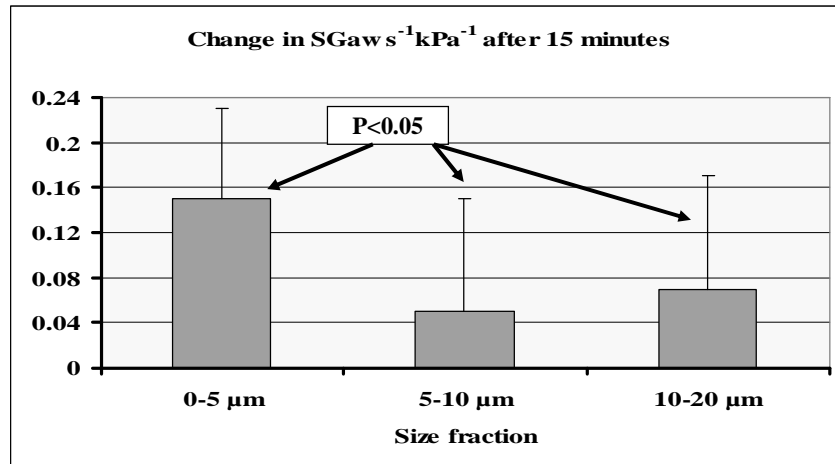
### FEV<sub>1</sub> RESPONSE TO CUMULATIVE DOSES OF TERBUTALINE SULPHATE FROM TURBUHALER DPI IN 12 ASTHMATICS

From Persson and Wiren 1989



**MEAN (SD) RESPONSE TO 250 µg TERBUTALINE  
SULPHATE FROM pMDI IN 10 ASTHMATICS**

From Rees et al 1982



Note: Size fractions were those placed in pMDI, not APSD of emitted aerosol

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**EFFECT OF CHANGES IN pMDI ACTUATOR ORIFICE DIAMETER  
ON ALBUTEROL BRONCHODILATOR RESPONSE**

From Evans et al 1992, available as abstract only

- § 200 µg albuterol given to 19 asthmatics via pMDI actuators with orifice diameters 0.23, 0.40, 0.50 and 0.59 mm
- § No data provided in abstract
- § Qualitative results:
  - Ø FPF differences statistically significant
  - Ø Statistically significant differences in PEF<sub>R</sub>, but not FEV<sub>1</sub>
  - Ø PEF<sub>R</sub> differences not considered clinically significant
- § Andersen cascade impactor “...offers a guide to clinical response and does not predict it accurately”

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### **PROBLEMS WITH PRIMARY DATA SET**

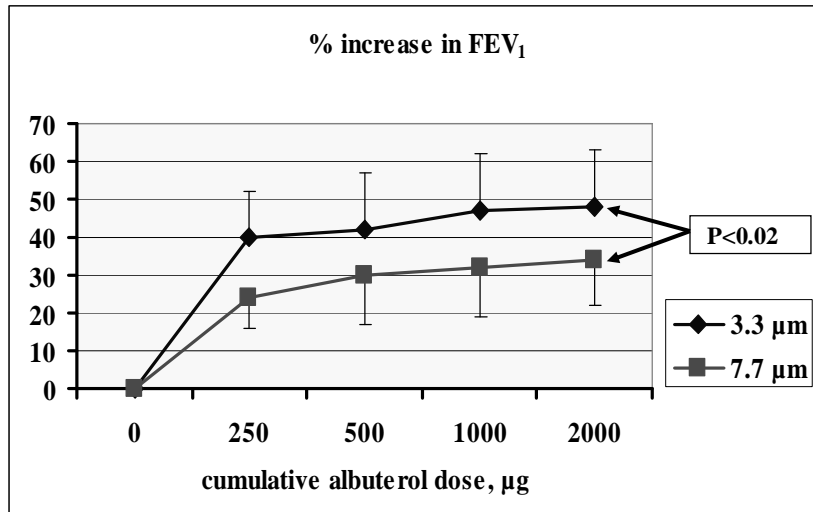
- § **Only three of five studies were designed to investigate relationship between particle size and clinical effect**
- § **Remaining two studies conducted for marketing purposes to show comparability between innovator and generic products**
- § **Full details of APSD not provided (usually limited to FPD)**
- § **Most studies used doses at or close to the top of the dose-response curve**
- § **Studies used small patient groups (max. 19), and some were probably underpowered**
- § **No inhaled corticosteroid data available**

### **NEBULIZER STUDIES**

- § **Eleven published studies have compared clinical responses to nebulized aerosols of different sizes**
  - Ø 8 used bronchodilators (X-over in up to 20 patients)
  - Ø 3 used rhDNase (100+ patients randomized to parallel groups)
- § **APSD changes engineered by using different nebulizers, varying the compressed gas flow rate used to drive the nebulizer, or both**
- § **Most studies unable to detect statistically significant or clinically significant changes in response**
- § **Two studies showing greater response to smaller aerosols also varied the inhalation manoeuvre**

**FEV<sub>1</sub> RESPONSE TO CUMULATIVE DOSES OF ALBUTEROL FROM TWO NEBULIZERS IN 8 ASTHMATICS**

Data from Johnson et al 1989



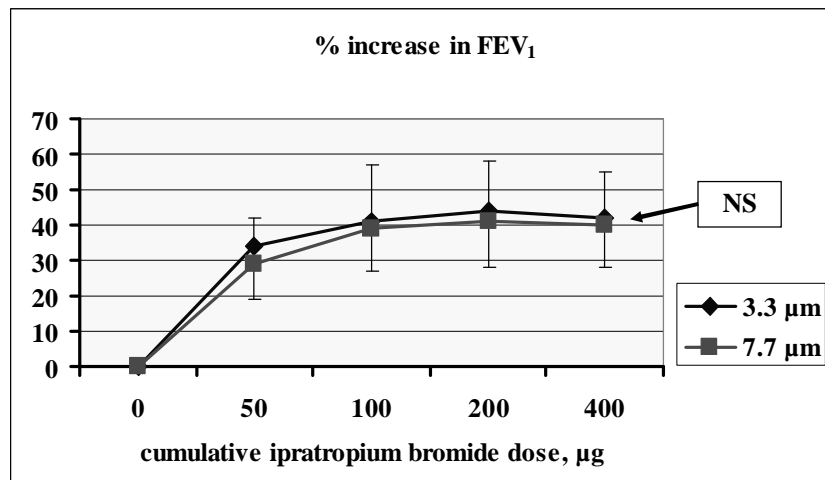
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**FEV<sub>1</sub> RESPONSE TO CUMULATIVE DOSES OF IPRATROPIUM BROMIDE FROM TWO NEBULIZERS IN 8 ASTHMATICS**

Data from Johnson et al 1989



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**MEAN (SD) CHANGES IN PULSE RATE AFTER INHALATION OF  
ALBUTEROL OR IPRATROPIUM BROMIDE IN 8 ASTHMATICS**

From Johnson et al 1989

	<u>3.3 µm</u>	<u>7.7 µm</u>	<u>P</u>
<b>Pre-albuterol</b>	<b>72.6 (4.8)</b>	<b>70.3 (5.5)</b>	<b>NS</b>
<b>Post-albuterol</b>	<b>78.1 (4.8)</b>	<b>76.5 (4.8)</b>	<b>NS</b>
<b>Pre-ipratropium</b>	<b>71.4 (6.2)</b>	<b>72.6 (4.6)</b>	<b>NS</b>
<b>Post-ipratropium</b>	<b>75.8 (4.8)</b>	<b>77.8 (5.8)</b>	<b>NS</b>

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**NEBULIZER CHARACTERISTICS AND SPIROMETRIC RESPONSES  
TO INHALED rhDNase IN TWO GROUPS OF OVER 300 CF PATIENTS**

Mean and range (or SD) data from Geller et al 1998

	<u>Neb 1</u>	<u>Neb 2</u>	
<b>Fine particle fraction (%)</b>	<b>83 (82-83)</b>	<b>51 (48-53)</b>	
<b>Output (%)</b>	<b>36 (33-40)</b>	<b>46 (45-48)</b>	
<b>Fine particle output (%)</b>	<b>30 (27-33)</b>	<b>23 (22-25)</b>	
<b>Nebulization time (min)</b>	<b>1.5 (1.3-2.0)</b>	<b>9.1 (8.1-10.3)</b>	
<b>% Δ FEV<sub>1</sub></b>	<b>4.3 (12.8)</b>	<b>2.5 (13.5)</b>	<b>P=0.06</b>
<b>% Δ FVC</b>	<b>2.6 (8.9)</b>	<b>1.2 (9.4)</b>	<b>P&lt;0.03</b>

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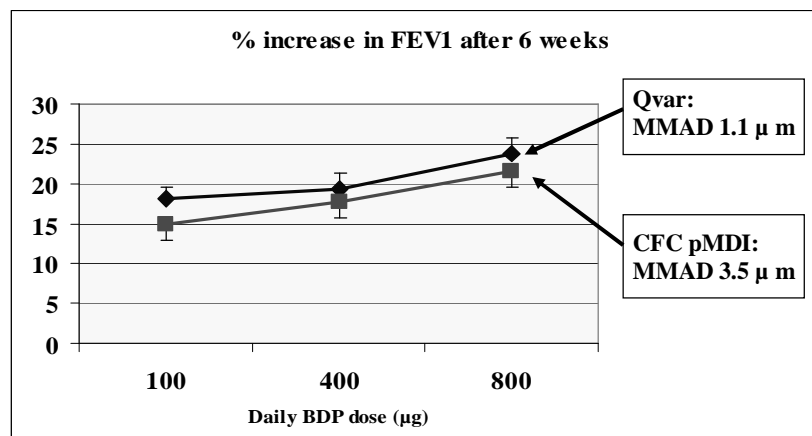
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## PROBLEMS WITH NEBULIZER STUDIES

- § The studies involved nebulizers, not “portable” inhalers (pMDIs and DPIs)
- § Most studies were carried out to answer a practical question: what is the clinical response when different nebulizers are operated in different ways?
- § Most studies provide very limited APSD data
- § Difficult to assess APSD / response relationship because of confounding variables
  - Ø Differences in nebulizer type, compressor, volume fill, nebulization time, drug concentration, inhalation manoeuvre
- § Doses often high enough to reach the top of the dose-response curve
- § Most of the studies were probably underpowered

## RESPONSE TO INHALED BECLOMETHASONE DIPROPIONATE IN 323 ASTHMATIC PATIENTS

Mean and SE data from Busse et al 1999

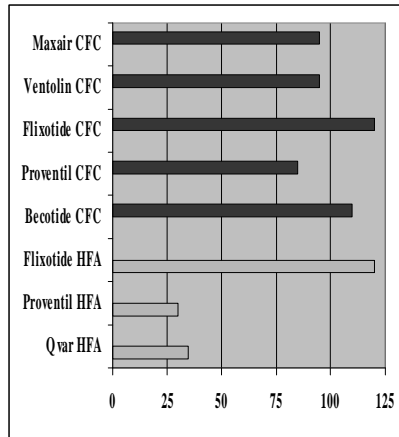


Qvar 2.6 times more potent than CFC pMDI

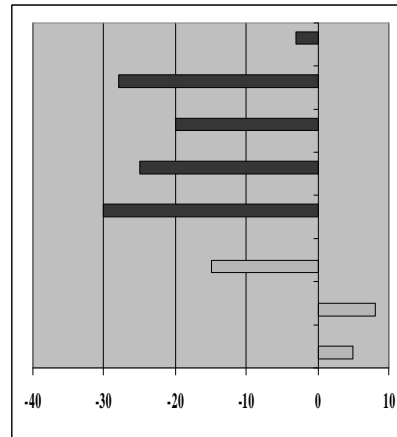
## PLUME CHARACTERISTICS OF pMDI SPRAYS

From Gabrio et al 1999

Maximum impact force (mN)



Minimum plume temperature (deg C)



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## PROBLEMS WITH CFC vs HFA pMDI COMPARISONS

§ **Difference in APSD may not be the only difference between the sprays**

Ø **Other spray characteristics (e.g. impact force and spray temperature) may change as well**

§ **Meta-analysis of > 50 studies comparing CFC pMDIs vs other inhalers (Hughes et al 1999)**

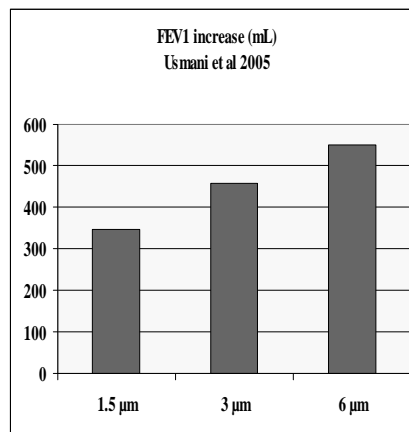
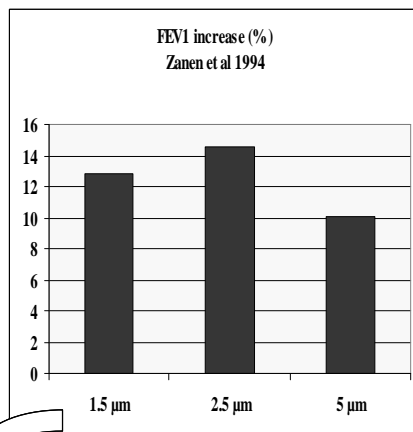
Ø **Most studies underpowered and used inappropriately high drug doses**

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## MEAN BRONCHODILATOR RESPONSE TO MONODISPERSE ALBUTEROL AEROSOLS



**Zanen et al: same effect in mild and severe asthmatics, and for albuterol, ipratropium bromide and combinations**

## PROBLEMS WITH MONODISPERSE AEROSOL STUDIES

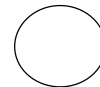
- § Results of similar studies from two major laboratories disagree about the nature of the relationship between particle size and clinical response to inhaled bronchodilators
- § Difficult to extrapolate results of studies with stable monodisperse aerosols of a fixed size to heterodisperse and unstable aerosols emitted from inhaler devices

**SOURCES OF VARIABILITY IN CLINICAL RESPONSE**

**SOURCES OF VARIABILITY IN CLINICAL RESPONSE**



APSD →



**SOURCES OF VARIABILITY IN CLINICAL RESPONSE**



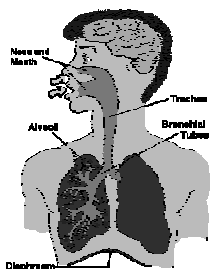
APSD  
→  
(INHALER / IMPACTOR)



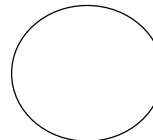
**SOURCES OF VARIABILITY IN CLINICAL RESPONSE**



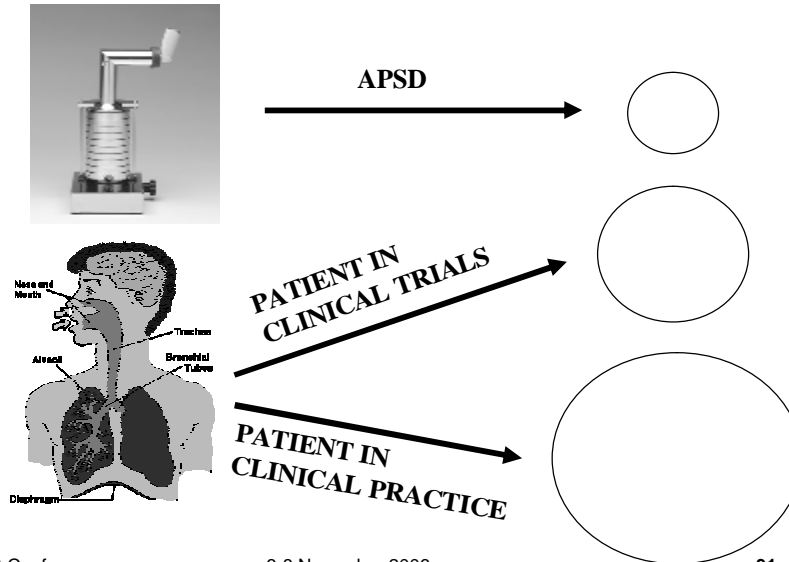
APSD  
→



PATIENT IN  
CLINICAL TRIALS  
→



## SOURCES OF VARIABILITY IN CLINICAL RESPONSE



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## CONCLUSIONS - 1

- § A range of published studies relate the APSD of pharmaceutical aerosols to therapeutic response – most data are at least 15 years old
- § In the context of assessing the APSD / response link, most published studies suffer from design problems and often present very limited APSD data
- § Most published studies were not conducted with the primary objective of examining the APSD / response relationship

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## CONCLUSIONS - 2

- § **Studies confirm that APSD influences therapeutic response to inhaled drugs**
- § **Some evidence that the relationship between APSD and clinical effect may vary from product to product**
- § **Even for well-established drugs, the change in APSD required for a clinically significant change in response cannot be deduced from public-domain information**

## CONCLUSIONS - 3

- § **Andersen cascade impactor “...offers a guide to clinical response and does not predict it accurately”**
- § **Variability in clinical response depends partly on the inhaler and on the APSD, but much more upon the patient who uses the inhaler**
- § **Trying to establish truly meaningful in vitro / in vivo correlations is challenging**

## **ACKNOWLEDGEMENTS**

**§ Review of data undertaken jointly with Kim Chan  
(University of Sydney)**

**§ Thanks to members of the IPAC-RS Cascade  
Impactor Working Group for their help and  
support**