

What Do Cascade Impaction Measurements Tell Us: *In Vitro* Aspects

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Context of Presentation

- This talk is a component of two presentations, the other of which will be given on clinical relevance of cascade impactor data by Dr. Steve Newman
- Your participation in the Q/A session afterwards is encouraged

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Multi-Stage Impactors: The Basics

- The equipment of choice for particle size analysis of most inhaler aerosols
 - Cascade impactors (CIs) determine *aerodynamic* particle size distributions (APSDs) by *size fractionating* the incoming aerosol
 - Most allow *direct assay* of collected active pharmaceutical ingredient (API)
 - They provide information *that may be indicative of lung deposition*

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Suitability Of CIs for OINDP Characterization

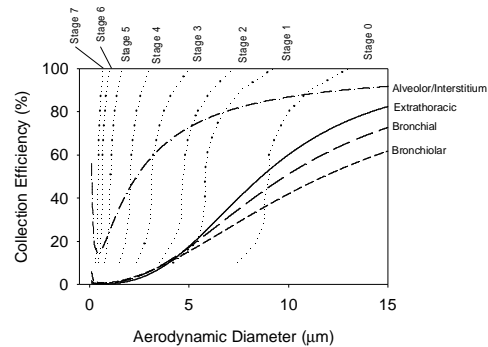
INHALER CLASS	SUITABILITY
pMDI	HIGH
DPI	HIGH
nebulizer	MODERATE
nasal MDI	MODERATE
aqueous nasal spray	LOW

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CIs are NOT breathing simulators !

- They operate at constant flow rate
- They do not simulate the environment in respiratory tract (T, RH etc.)



Dunbar and Mitchell. *J. Aerosol Med.*, 2005; 18(4): 439-451
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- Attempts have been made to link CIs to breathing simulators, but the approaches are complex and more suited to research than routine product quality assessment
- **EXAMPLES:**
 - Brindley *et al.* *J. Pharm. Pharmacol.*, 1994; 45: 1-35
 - Finlay and Zuberbuhler, *Int. J. Pharm.*, 1998; 168: 147-152
 - Foss and Keppel, *Respir. Care*, 1999; 44: 1474-1485

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Then What do CIs do?

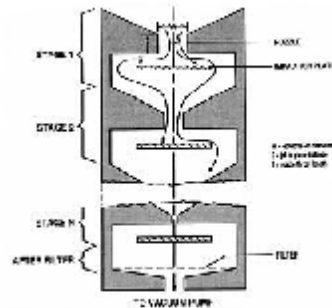
- They have size-selectivity in the critical range defining likely deposition in the airways and alveoli of the lungs:
 - At least 5 data points between 0.5 and 5 μm aerodynamic diameter (Marple et al. *J. Aerosol Med.* 2003; 16(3):283-299)
 - 1 or 2 data points at larger sizes associated with oropharyngeal deposition
 - Low pressure designs (*i.e.* ELPI offer significant resolution for nano-particles – down to 0.05 μm in size
 - Nanoparticle deposition occurs by diffusion
 - There is increasing interest in this size range

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What are the Critical Issues Concerning CI Data

- **Size Resolution:**
 - CI design considerations
- **Operating conditions:**
 - Key variables
 - Recovery of API
 - Operator related issues
- **Data analysis:**
 - Metrics
 - Pitfalls
 - APSD profile comparisons



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Key References to Impactor Theory

- Marple and Willeke. *Fine Particles* 1976:411-466:
 - Impactor aerodynamics, Stokes number and particle size
- Rader and Marple. *Aerosol Sci. Technol.* 1985;4:141-156; *Aerosols* 1984:123-126
 - Ultrastokesian flow, effect of gravity
- Fang *et al.* *J. Aerosol Sci.* 1991;22: 403-415
 - Cross-flow in multi-orifice stages

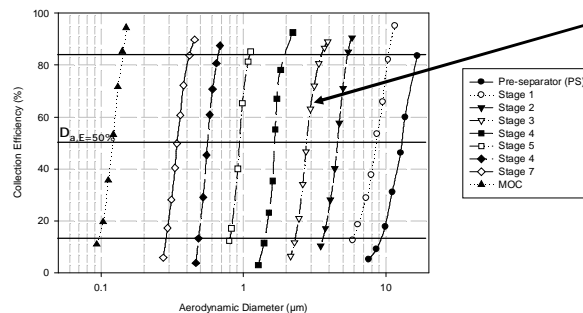
Review on CI use for inhaler aerosol size characterization by Mitchell and Nagel: *J. Aerosol Med.* 2003;16(4):341-377
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Impactor Size Resolution

- The resolution of a CI is dependent upon the sharpness of cut for each of the stages:

NGI calibration at 60 L/min



Stage GSD < 1.2 is ideal

$$GSD = \sqrt{\frac{E_{84.1\%}}{E_{15.9\%}}}$$

$d_{0, E=50\%}$ is the calibration constant for each stage
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Impactor Theory: What does it tell us about CI resolution?

- For a well-designed CI with circular orifices, the critical particle Stokes number (\sqrt{St}) defining collection is close to 0.495*
 - stage flow Reynolds number (Re_f) in range 500-3000
 - ratio of nozzle-to-plate/cup distance (S)/to nozzle width (W) in range 1-10 :

$$St = \frac{4r_p QC_p d_p^2}{9n\mu W^3} = \frac{4r_{ae} QC_{ae} d_{ae}^2}{9n\mu W^3}$$

Marple *et al.* *J. Aerosol Med.*, 2003;16:283-299

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- Re_f for each stage should be within 500 and 3000 to optimize sharpness of cut (size resolution)
 - There is evidence from the ACI and NGI that the lower limit can be relaxed considerably (< 100?)

$$Re_f = \frac{r_a UW}{m}$$

- The cross flow parameter (X_c) should be < 1.2 to avoid non-uniformity of deposition beneath a multi-orifice plate:

$$X_c = \frac{nW}{4D_c}$$

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How do the Pharmacopeial CIs Measure Up?

- The Andersen 8-stage Impactor (ACI) and Next Generation Pharmaceutical Impactor (NGI) generally meet these criteria within their recommended operating flow rates:
 - 28.3 L/min for standard ACI
 - 60 and 90 L/min for modified ACI configurations*
 - 30 and 100 L/min for the NGI**†

* Nichols *PharmEuropa* 2000;12(4):585
Nichols *et al. J. Aerosol Med.* 1998;11(S1):133-138

** Marple *et al. J. Aerosol Med.* 2003;16(3):301-324

† *may be used at 15 L/min without pre-separator and with filter in addition to MOC: Marple et al. J. Aerosol Med.* 2004;17:335-343

What is the Importance of Operating Conditions?

- The CI measurement process is complex to undertake and there are many sources of bias and imprecision
- These have been systematically reviewed by Christopher *et al.*:
 - *J. Aerosol Med.*, 2003;16(3):235-247

Considerations for the Development and Practice of Cascade Impaction Testing, Including a Mass Balance Failure Investigation Tree

THE FINE PARTICULATE DISTRIBUTION MASS BALANCE WORKING GROUP
DAVE CHRISTOPHER, CHAIR, PAUL C. JURY, PETER HILL, DONALD W. COLE,
KENNETH FURNKRNANZ, MELISSA M. CHAN, ANNE B. BELL, SAKI MIKI, PHILIP
SVETAKA, YAPUSI NA, PHILIP OLYVIN MITCHELL, PHILIP BRIAN ROGERS, PHILIP
THELEN, KIRILANO BELLUCCI, FERENC BOLGAS, HUIJIE YU, SHONG PHILIP
and BRUCE WYKA, SECRETARIES

Factors Causing Variability of Impactor Data

air flow control: $\pm 5\%$

- calibration
- setting
- leakage

environmental: $\pm 5\%$

- T & RH
- electrostatic charge
- coating on collection surfaces

geometry: $\pm 1\%$

- nozzles
- induction port

wall/internal losses $\pm 2\%$

factors are either modifiable or non-modifiable for each determination

courtesy: S.C. Nichols, sanofi-aventis

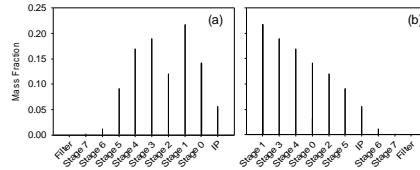
- An understanding was gained by the PQRI PSD Mass Balance WG as to how each variable might impact on APSD and the mass balance (MB) that is also obtained from a CI measurement
- If the principles in this 'Good CI Practices (GCIP)' document are applied, the resulting CI APSD data are likely to be consistent and representative of the aerosol being sampled

CI Data Interpretation: 3 Ways*

* Dunbar and Mitchell. *J. Aerosol Med.* 2005; 18: 439-451

- 1. Mass distribution as a nominal function of deposition sites in CI system:

- Non-sizing and sizing components of the measurement system are considered
- Profile analysis in this way is popular:
 - generic vs. innovator products
 - product quality considerations



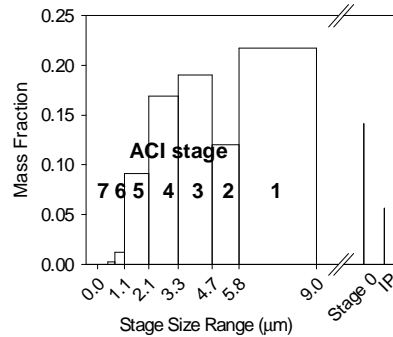
no information is provided that links mass with d_a

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- 2. Link the mass deposited on size-fractionating stages ($M_{\text{stage } 1 \dots n}$) with the range of operation of stage (stage width):

- relationship between CI collection characteristics and mass for the size-fractionating stages
- Useful for comparing data all from one impactor type (e.g. ACI), particularly when almost all the mass ex inhaler is collected within the CI



No association between data from non-sizing components and the stage size range scale

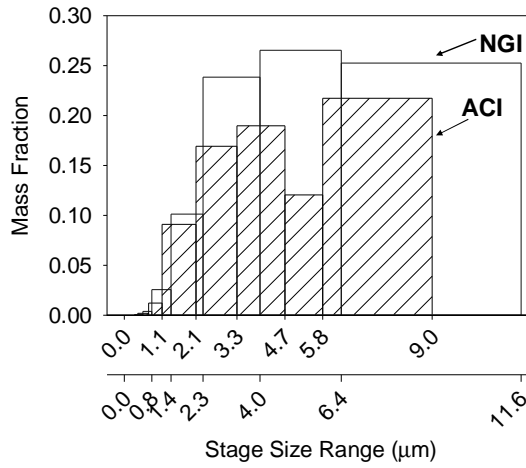
APSD has distortion if the magnitude of the range (width) varies from stage to stage

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It is also difficult to compare data from different CI designs

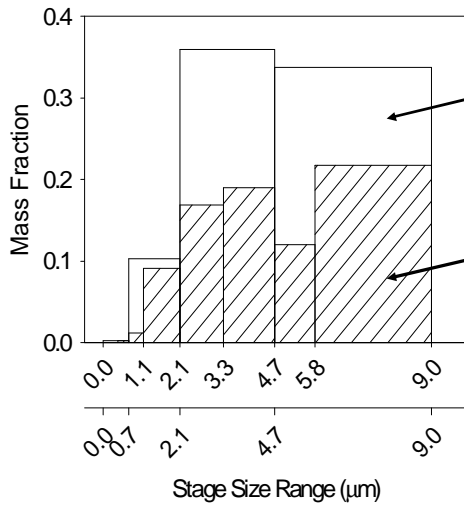
model aerosol
MMAD = 5.0 μm
GSD = 2.0



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• and stage grouping may mislead!



2-stages
per group
- uni-modal

1-stage
per group -
apparently
bi-modal

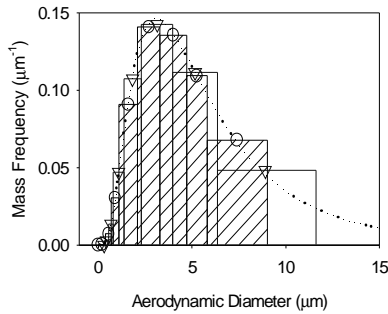
The aerosol
appears not
to be identical
when it is

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- 3. Calculate the true functional relationship between $M_{\text{stage 1...n}}$ and d_a :

$$\text{Mass Frequency } (d_{a,i}) = \frac{m_i}{M_{ED}} \frac{1}{\Delta ECD_i}$$

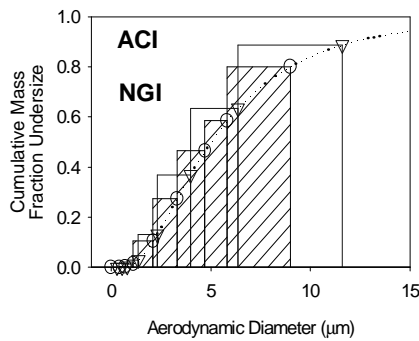


There is a functional relationship between mass and d_a

Comparisons between data from CIs of different type are self-evident

Transitioning from other CIs to the NGI is easy to do

The same data can also be expressed in cumulative form:



MMAD = 5.0 μm
GSD = 2.0

- Both ACI and NGI provide an identical relationship even though their stage ECDs differ
- Data from other impactor designs can be compared easily

Derived Metrics

- FPF – fine particle fraction:
 - typically mass < 5 $\mu\text{m } d_a$ (Ph.Eur. definition)
- EPF – extra fine particle fraction:
 - typically < 1 $\mu\text{m } d_a$
- CPF – coarse particle fraction:
 - typically mass > 5 $\mu\text{m } d_a$

No assumption about form of APSD is made

- MMAD – mass median aerodynamic diameter:
 - 50th percentile of cumulative APSD
- GSD – geometric standard deviation

$$= \sqrt{\frac{d_{84.1}}{d_{15.9}}}$$

GSD assumes log normal APSD

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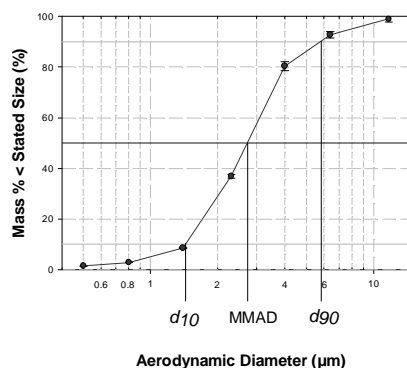
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- If the APSD is uni-modal, but not log-normal, an alternative approach to the use of GSD is to calculate a relative span factor (RSF):

$$RSF = \frac{d_{0.9} - d_{0.1}}{MMAD}$$

where $d_{0.9}$ and $d_{0.1}$ are the sizes corresponding to the 90th and 10th mass percentiles respectively

Cumulative Mass-Weighted APSD



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Calibration Matrix Method for CI Data Interpretation

- Iterative procedures that calculate APSD taking into account the complete stage collection efficiency curve functions rather than just the $d_{a,E=50\%}$ values:
 - Advocated by Marjoral *et al.* *Aerosol Sci. Technol.* 2006;40:672-682 for nebulizer-produced aerosols
 - Mainly a problem with older designs of CIs with asymmetric collection efficiency curves
 - The effect on metrics such as FPF can be large
 - Requires further investigation

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APSD Profile Comparisons

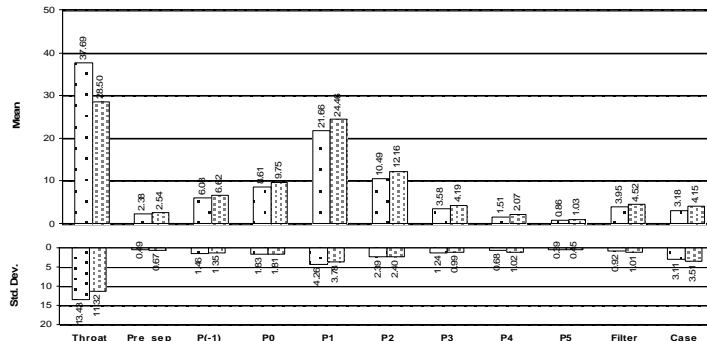
- Of interest for the evaluation of bioequivalence of generic compared with innovator products
- Regulatory interest in the USA is focused on the development of robust statistical methods to enable reviewers to judge equivalence or otherwise
- The PQRI PSD Profile Comparisons WG has worked on this topic since the Fall of 2001, focusing on ACI-measured data

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Example of a PSD profile comparison:

- Mean and standard deviation of the mass collected on each component of the CI train are compared side-by-side



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- The PQRI group have used statistical methods to evaluate APSD comparability:

- Chi-square (χ^2) ratio
- Impactor-sized mass (ISM)

- Supported by member-based comparisons of 55 scenarios, based on likely variations in product performance
 - 'eye-ball' and more rigorous judgments

ID	Scenario	WG Assessment (%)	Chi Square (%)	ISM (%)	Combined (%)	Difference WGS Method
1	1a	1.00	1.00	0.72	0.90	0.50
2	1b	0.73	1.00	0.22	0.32	0.57
3	1c	0.82	1.00	0.19	0.61	0.66
4	1d	0.90	1.00	0.22	0.60	0.60
5	1aa	1.00	1.00	0.19	0.61	0.60
6	1ab	0.73	1.00	0.47	0.40	0.24
7	1ac	0.38	1.00	0.21	0.01	0.25
8	1ad	0.83	1.00	0.10	0.60	0.60
9	1ae	0.93	1.00	0.10	0.60	0.60
10	2a	0.74	1.00	0.16	0.64	0.61
11	2b	0.53	1.00	0.32	0.32	0.42
12	2c	0.21	1.00	0.16	0.08	0.66
13	2aa1	0.71	1.00	0.22	0.38	-0.17
14	2aa4	0.54	1.00	0.10	0.00	0.16
15	2aa1	0.53	1.00	0.24	0.24	-0.24
16	2aa1	0.23	1.00	0.22	0.00	-0.68
17	2aa2	0.54	1.00	0.22	0.00	-0.26
18	2aa2	0.23	1.00	0.22	0.00	-0.68

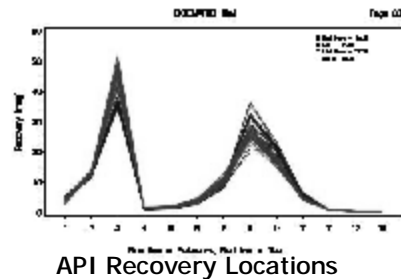
Data for 18 of the 55 scenarios for hypothetical beta₂ agonist

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- The WG concluded:
 - The combined effects of χ^2 and ISM tests improved the discriminating for bioequivalence in some instances
 - In certain instances, the χ^2 test alone appears sufficient
 - In relatively rare instances, neither test nor their combination is adequate and there is therefore the necessity for human judgment under such circumstances

This example proved difficult to agree on equivalence



- These findings appear to indicate that carefully measured CI APSD data can tell us something about the bioequivalence of the product:
 - However, the influence of data quality (variability from whatever cause) on the sensitivity of such comparisons remains to be explored

Where Next?

- In a Quality by Design (QbD) environment, the manually-operated CI has significant limitations:
 - It is labor intensive with many steps for a successful APSD determination
 - It is incapable of real-time measurements, ideally required in multivariate studies (Design of Experiments) that are necessary to identify design space for product and inhaler device
 - Automation may help speed up the process as well as reduce data variability

- The potential exists for developing *in vitro* correlations with appropriate PSD measurement techniques having real time capability, with the CI as benchmark:
 - *i.e.* laser diffraction for solution formulations delivered by pMDI or nebulizer
- However, such correlations would need to be developed on a product-by-product basis
- In the future, the role of CIs may therefore shift to providing benchmark measurements against which APSD data from faster techniques are compared

Concluding Remarks

- Carefully executed CI measurements can provide APSD data that enable judgments to be made concerning inhaler product quality:
 - may include assessments of bioequivalence in APSD profile comparisons
- The CI method will remain the mainstay for APSD measurements for the foreseeable future

Acknowledgments

The author would like to acknowledge the technical support received from colleagues in both PQRI Mass Balance and Profile Comparison WGs