Measuring Particle Size Distributions

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Inhalation Drug Development

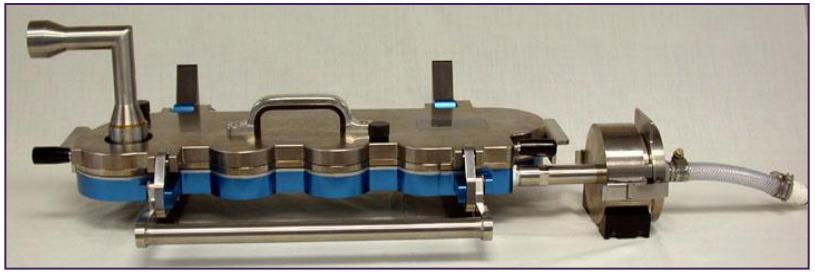
28/29th Sept 2010

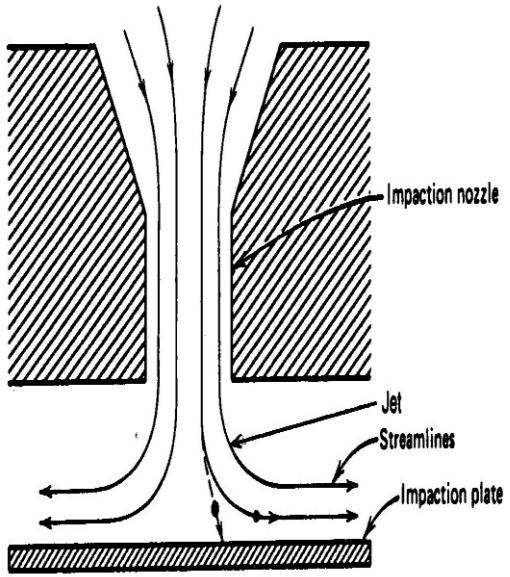
AstraZeneca

life inspiring ideas

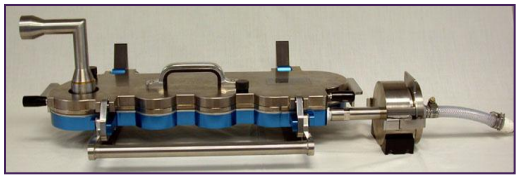
The Question Posed

- Impactor Testing – “Can we reduce the analytical burden?”
  - What do we currently do?
- Any alternatives to Full Resolution Cascade Impaction?
  - Abbreviated Impactor Measurements Initiative (AIM)
  - Non-Impactor solutions?





Our Starting Point

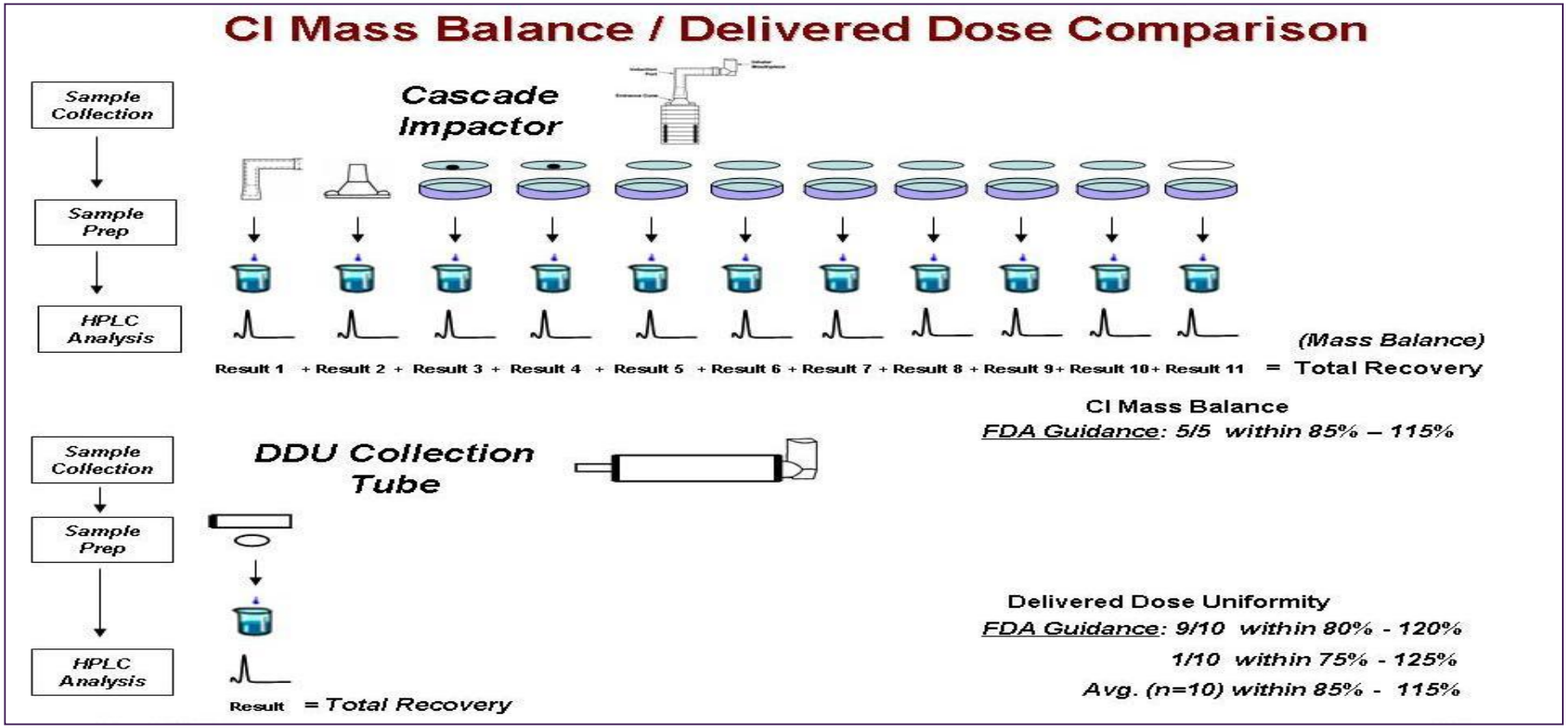


- Assessment of particle size distribution from oral inhaled products (OIPs) is by multi-stage cascade impactor (CI)
- Gold standard method:
  - Provides *aerodynamic* size
  - Traceability to drug mass (Selective Technique)
  - System suitability verifiable through mass balance
    - Though cumulative error in drug recovery can adversely effect this

…but full resolution CI measurements are complicated and therefore both time-consuming and prone to error
[*Bonam* et al. *AAPSPharmSciTechnol. 2008;9:404-413*]

Full Resolution CI Measurements

- Primary focus is on assessing changes in sub-fractions that are believed pertinent to predict particle deposition in respiratory tract
- Secondary focus on the APSD itself:
  - Often assumed log-normal and uni-modal in estimates of MMAD and GSD



Analysis Efficiency – NGI vs ACI

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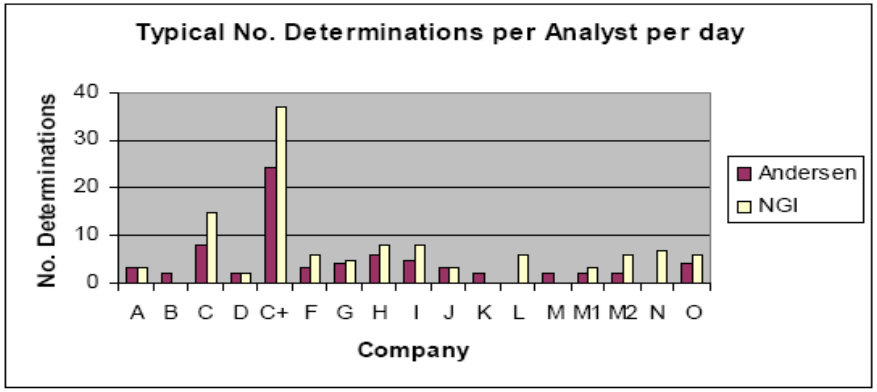
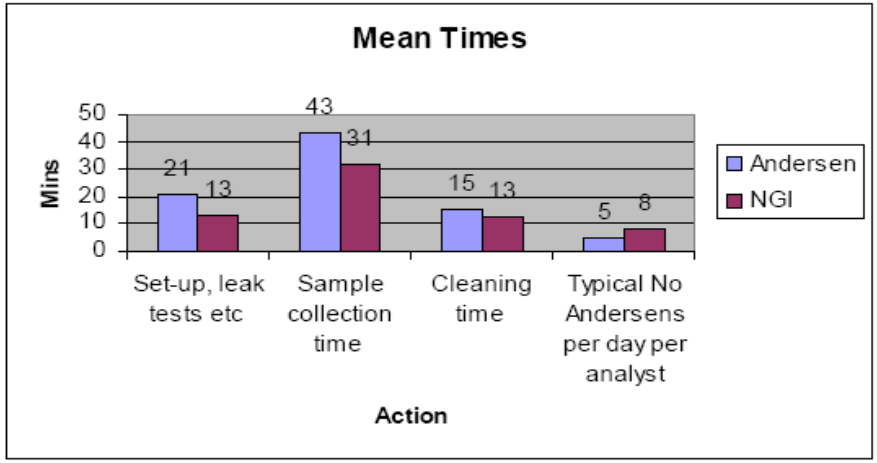
- 14 Companies took part (coded)
- Overall NGI Showed improvements in throughput
- Many NGI's not yet in use

TYPICAL No. PER ANALYST PER DAY



MEANS

- Total mean 79 mins & 59 mins for ACI & NGI respectively (NGI 21% quicker)
- 5 ACI & 8 NGI per analyst per day (50% more)



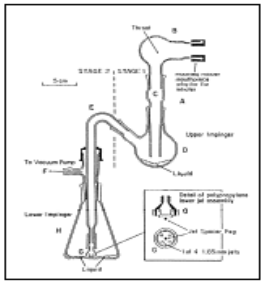
Can we simplify this process Further?

Abbreviated Impactor Measurements (AIM)

- A simplified Impactor based approach to the problem of inhaler Aerosol Particle Size Characterisation
- AIM is a Concept currently utilising a number of different Measurement options
- Fractions like Course, Fine and Extra Fine Particle mass (CPM, FPM & EPM) provide simple and useful performance information
  - AIM is an ideal approach for determining these
  - Simplified measurements cf full CI
  - Better design space coverage improved decision making (QbD)

Examples of AIM Systems

Twin Impinger



MSP Fast Screening Impactor

Courtesy MSP Corp.

Westech Short-Stack Fine Particle Dose Impactor

Courtesy Westech Instruments Inc.

Copley Short-Stack Fast Screening Andersen Impactor

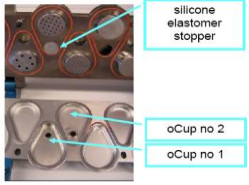
Courtesy Copley Scientific

Courtesy MSP Corp.

Reduced NGI (R-NGI)

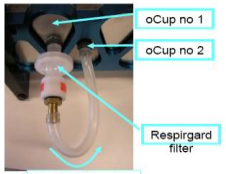
- Use of two oCups is convienient
- Place them after each other on suitable stage positions
- Place a filter after oCup no 1
- Don't forget to plug the normal air passage

Courtesy Mårten Svesnnson, AZ Lund



NGI with deeper cups at stages where particle collection is not required

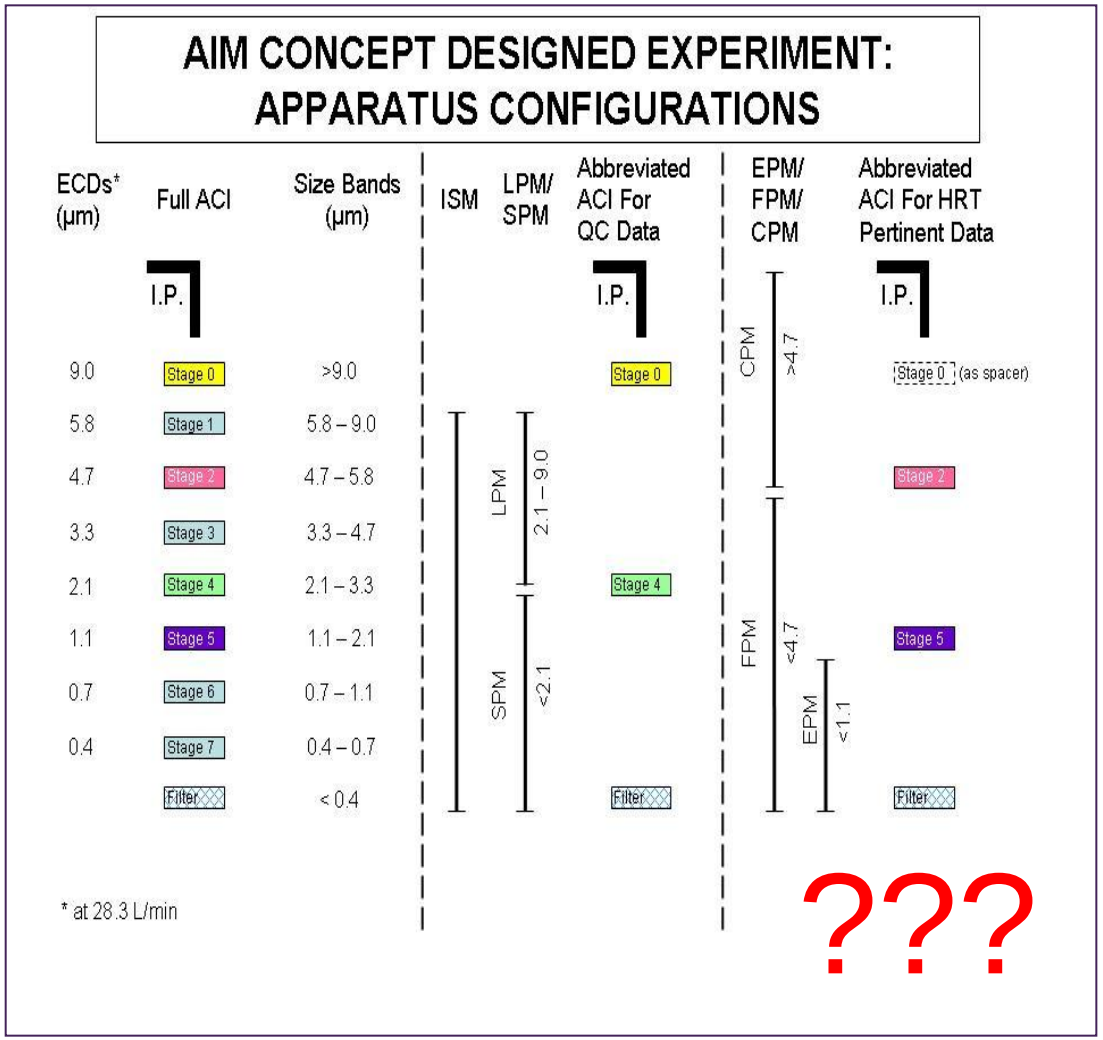
- Coarse/fine fraction size separated in NGI stage(s) before first o-CUP
- Flow leaves o-CUP floor
- Fine particle fraction collects in filter
- Flow cleaned of particles is returned to the NGI via second o-CUP



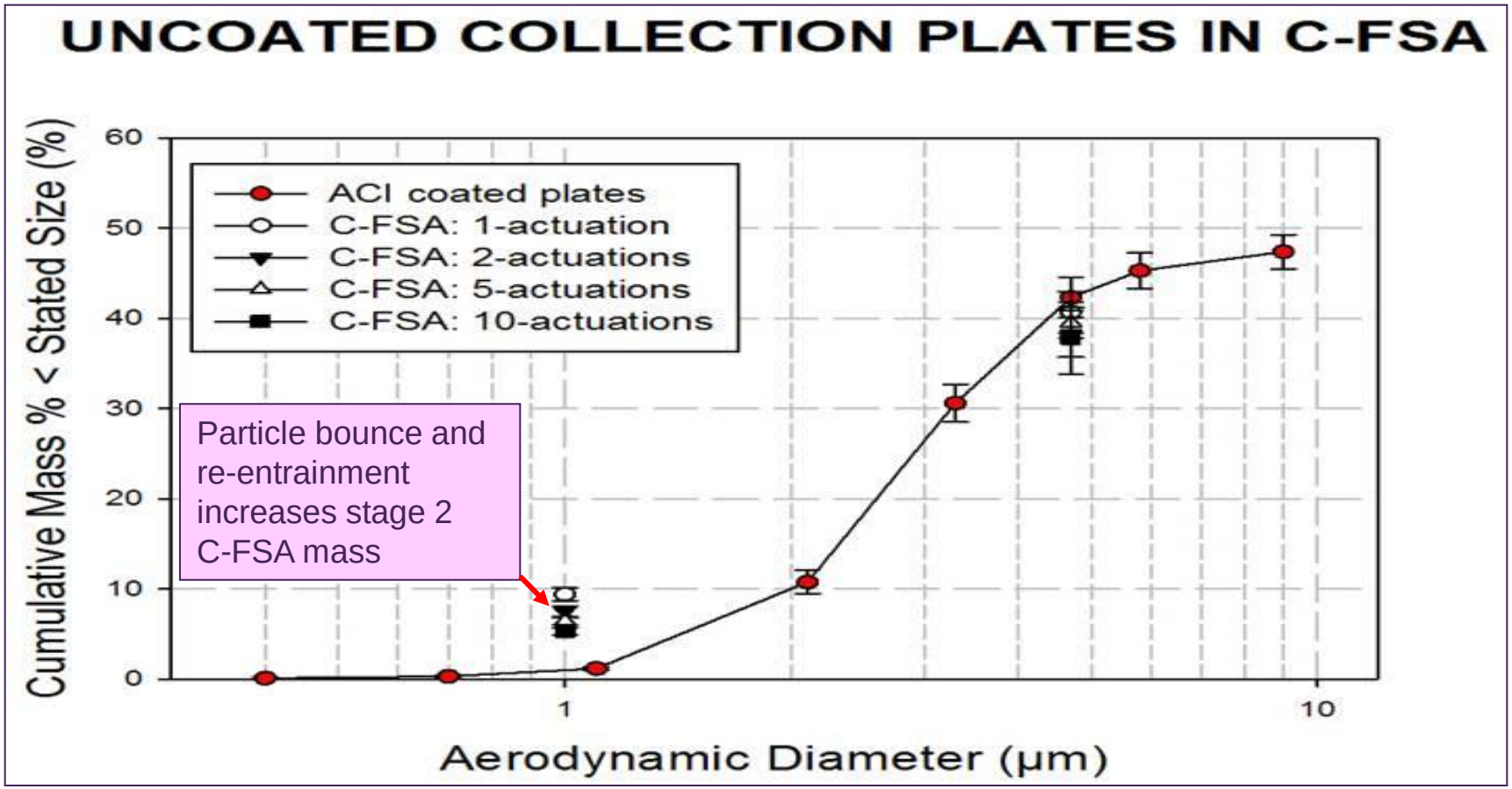
Courtesy Mårten Svesnnson, AZ Lund

Why Consider AIM Systems?

- Faster Analysis
  - 3 – 4 stage measurement cf ~ 9 - 11 stage determinations
- Flexibility
  - QC or Human Respiratory tract pertinent measurement?
  - Further enhanced by using Airway "*Throat*" models eg
    - Oropharygeal (OPC),
    - Finlay Alberta models
  - Breathing simulator/Mixing Inlet measurements?



Coating of collection plates for ACI and C-FSA is *essential* for the most accurate work

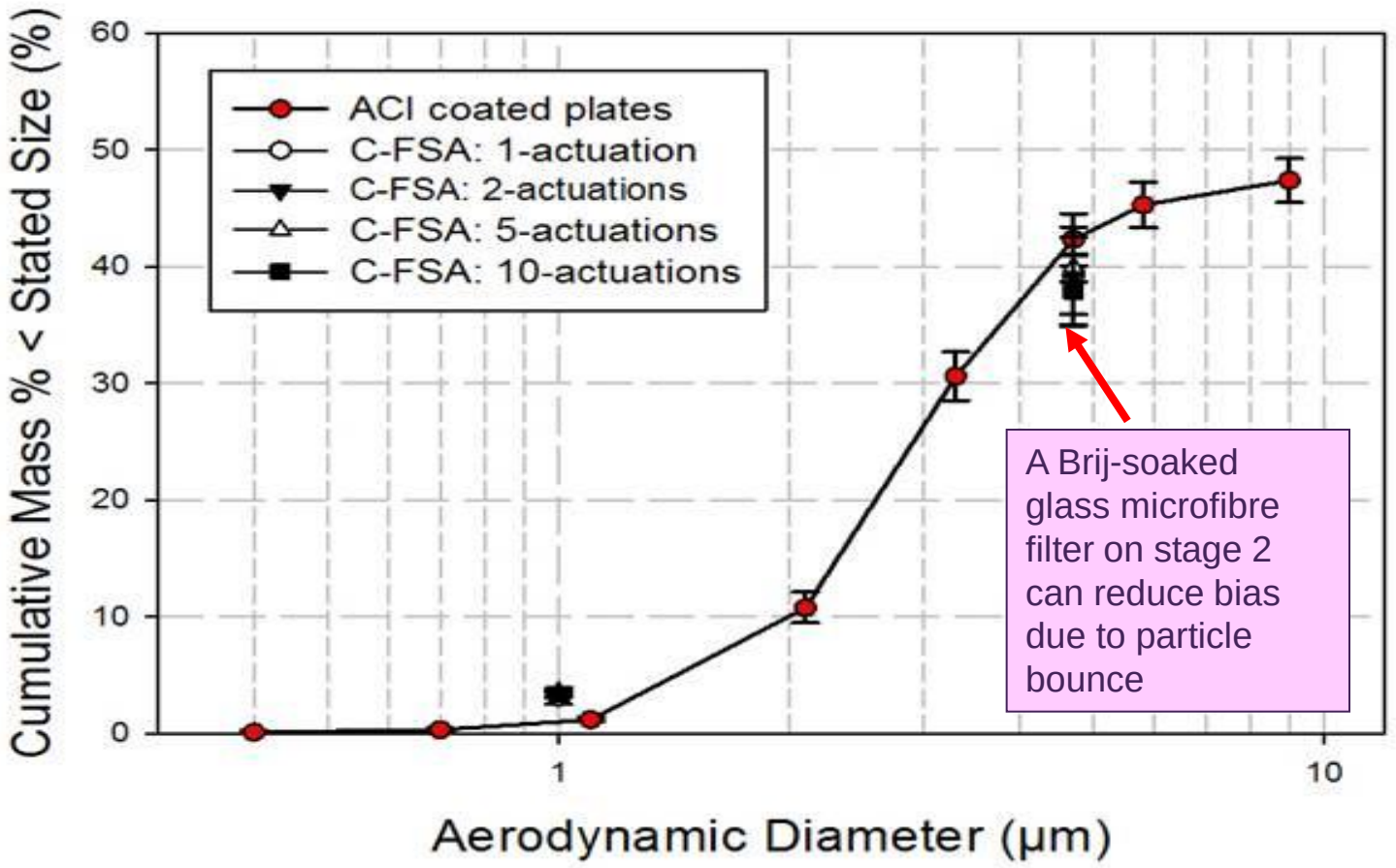


EPAG European Pharmaceutical Aerosol Group

IPAC-RS

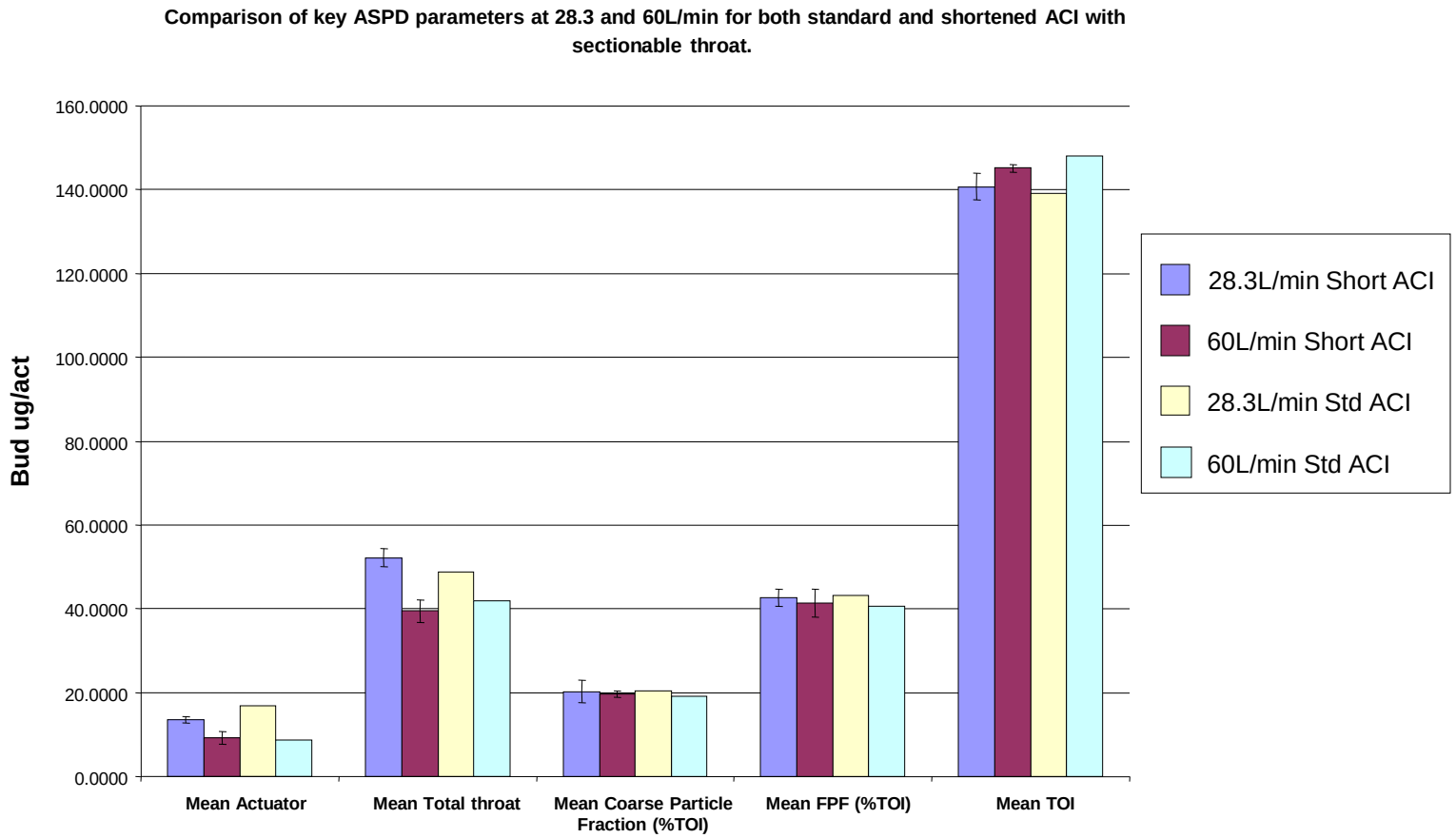
Substantial equivalence has been achieved between C-FSA and ACI

BRIJ 35 COATED COLLECTION PLATES IN C-FSA

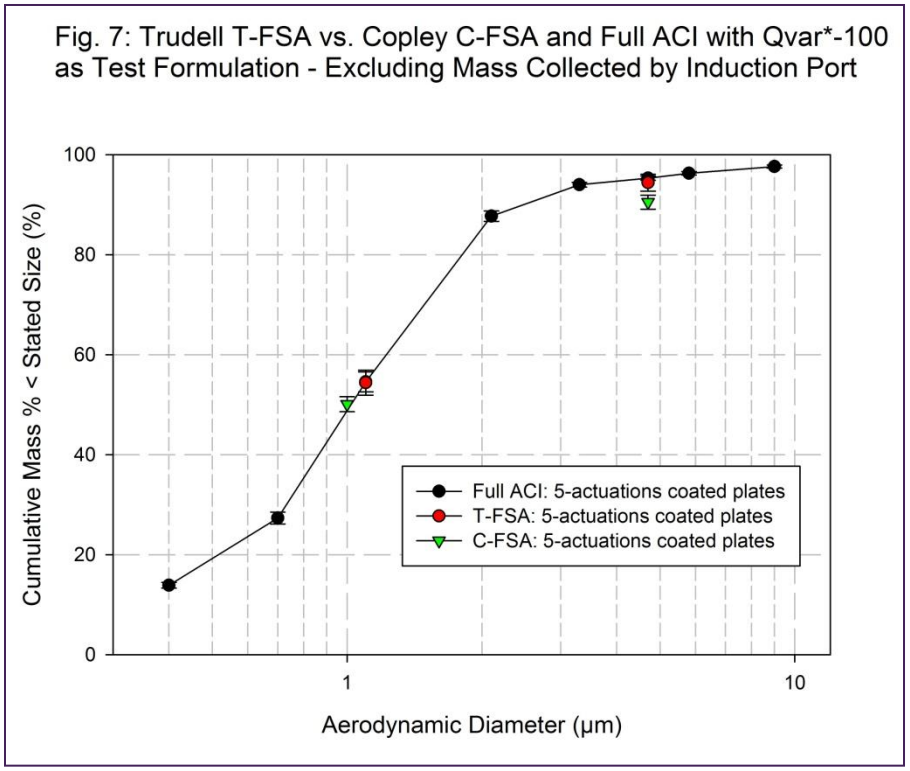


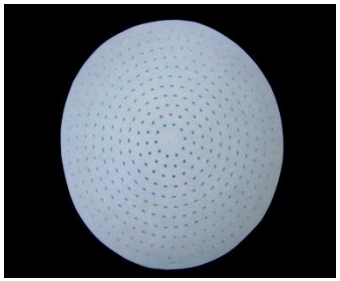
Flow rate effects - Short Stack ACI (AZ)

- Stack composition – IP/Stage 0/Stage 2/ stage 7/Filter
- Stage 1 substituted for stage 2 @ 60 Litres min^{-1}

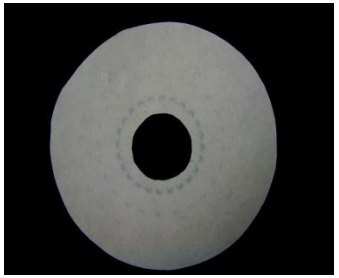


Solution MDI Evaporative Effects – QVAR*





Liquid EtOH deposits on stage '1' of C-FSA



Liquid EtOH deposits on stage '0' of full ACI

'empty' stage '0'

- 8% v/v ethanol in Qvar* has small, but measurable impact on FPF
- Can be eliminated by use of empty stage '0' above stages 2 and 5 in abbreviated design

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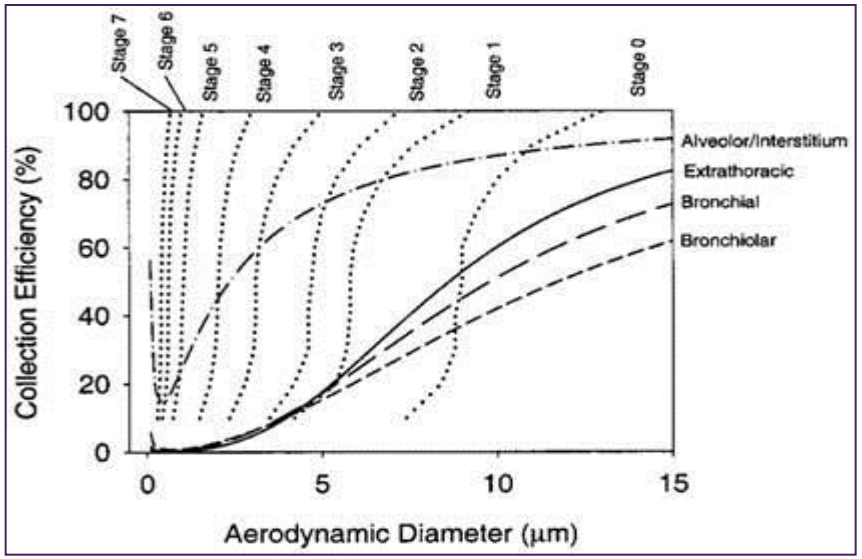
CI Stage Resolution cf Respiratory Tract (IVIVC)

- **Multi-stage CI selectivity (resolution) >> size-related deposition selectivity in human respiratory tract (HRT)**

- The multi-stage CI is therefore **NOT** an analogue of the HRT with regards to describing particle deposition



Respiratory tract deposition (ICRP-66) model with collection efficiency curves for the Andersen 8-stage cascade impactor (ACI) operated at 28.3 L/min superimposed

- from Dunbar and Mitchell (2005) J. Aerosol Med., 18:439-451

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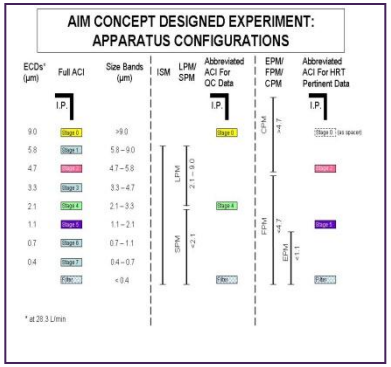
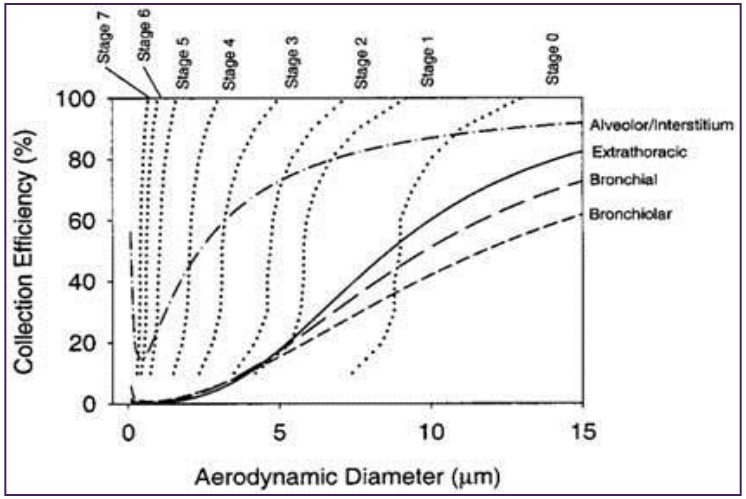
In Vivo - In Vitro Correlation (IVIVC)

- Selective use of lower stages with OPC Induction ports can be applied

  eg OPC Consortium/Finlay Alberta Models



- Does this provide enough sensitivity especially in the CPM to predict *In Vivo* performance?
- Does the AIM approach make adequate allowance for changes in airflow rate?



Do we need an Impactor?

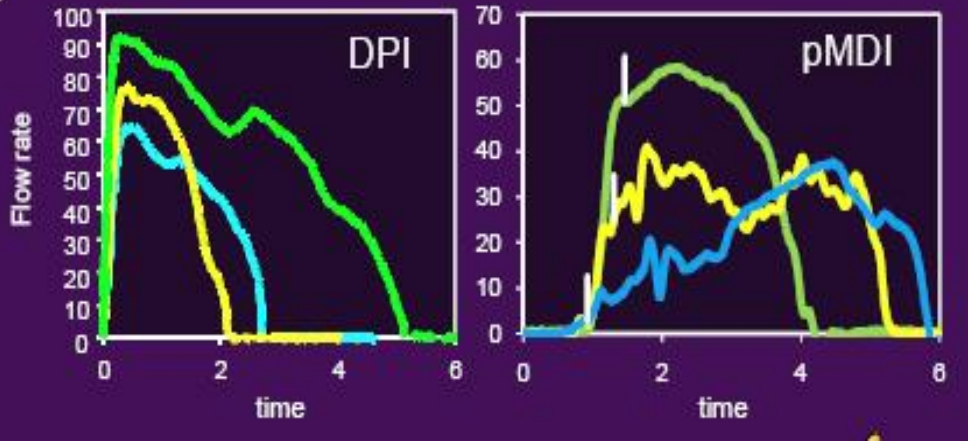
Predict lung dose using ex OPC filter dose with simulated breathing profiles - a viable alternative?

(RDD 2010 Olson, Borgstrom, Svensson et al)

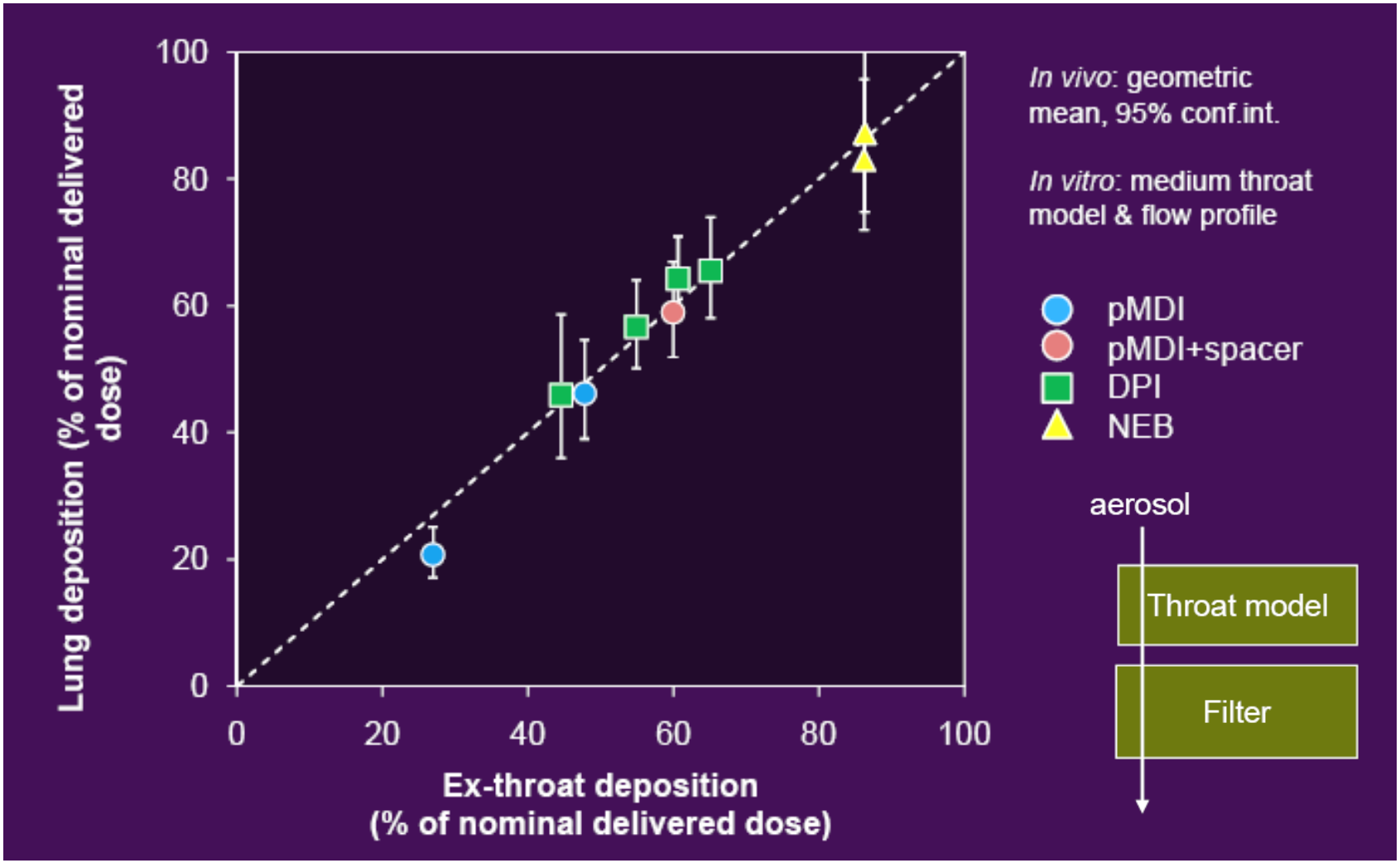
Simulating *in vivo* conditions

- Throat models
  - Statistically selected MRI derived physical models of adult subjects inhaling through objects
- Flow profiles
  - Device specific statistically selected profiles, or summary profiles
- Handling
  - According to patient instructions

Burnell *et al*, *J Aerosol Med* 2007



Predicted deposition resembles actual

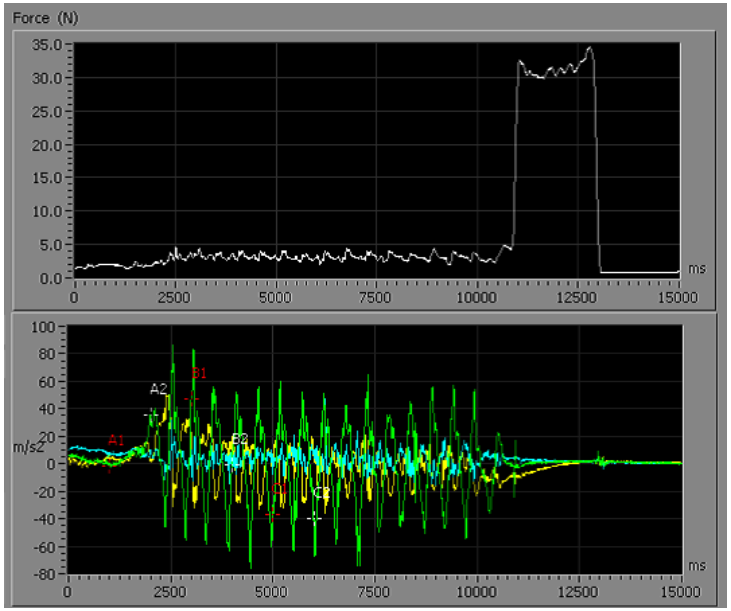


Olsson *et al*. (2010) Respiratory Drug Delivery 2010, pp. 225-234

What else can we do?

- Ensure the method requirements are consistently met via control of the identified critical analytical method parameters.

- Appropriate Analytical test method validation/SST's
  - API recovery from impactor (mass balance checks/re-wash Strategies)
- Standardized device handling
  - Shake/Fire for pMDI
  - Continued training and monitoring is also important for OINDPs
- Product specific issues
  - Direct impact of validation
    - Product properties
  - Electrostatics – DPI?



Measurement of Operator shake/fire inputs

Could we take the impactor out of the equation?

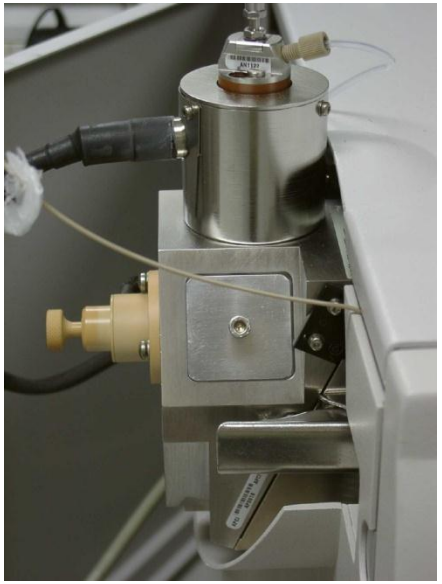
Direct Spray MS (direct sample induction)

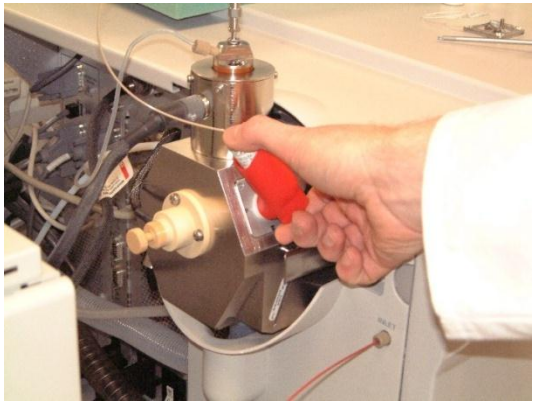
- Current screening techniques like APS/ELPI/Spraytec lack specificity to drug components in the formulation
- Could Mass Spec selectivity offer a solution to these issues?
  - Droplet size range from pMDI similar to that produced by an LC-MS nebuliser spray
  - If so how would we approach it?
  - LC-MS?
  - No chromatography?
- Or possibly direct sample induction?
  - Can we spray the pMDI directly into an MS spray chamber?

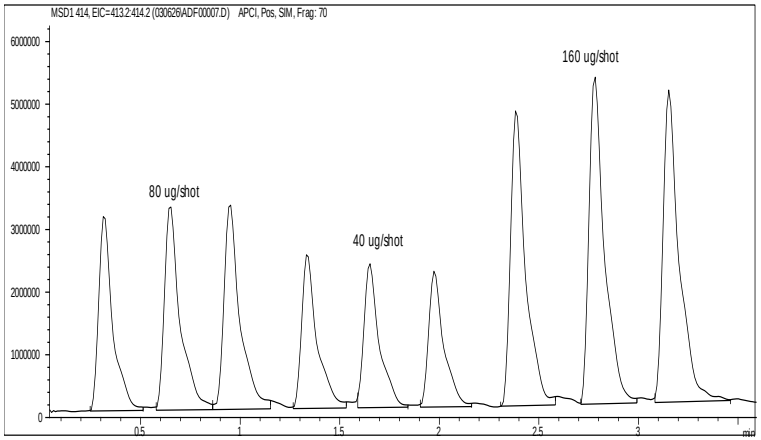
Pat Ref –WO/2008088270

How it works

- Very Simply!
- The pMDI actuated directly into the spray chamber of an LC-MS

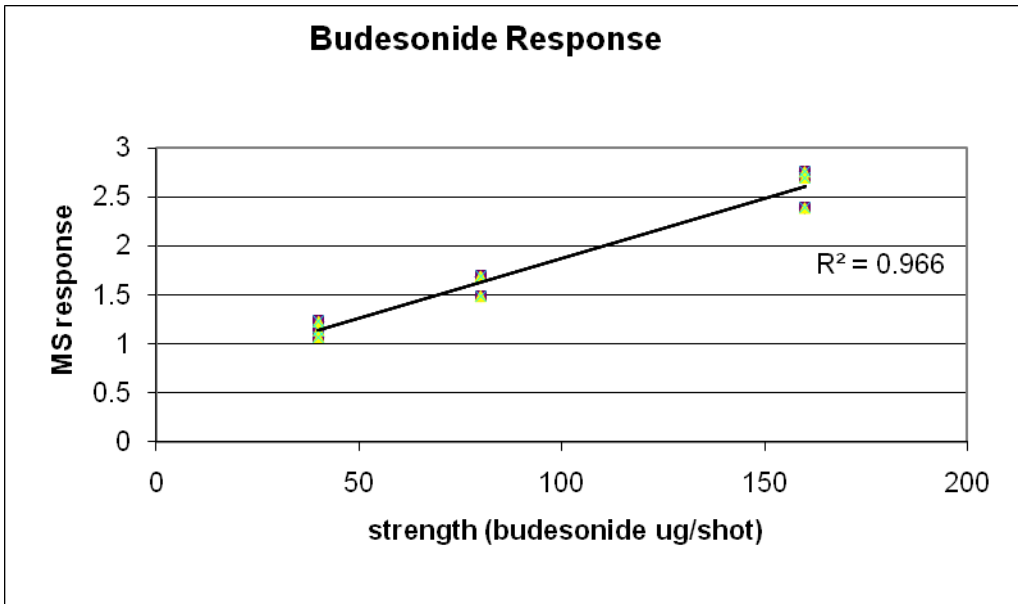






Initial Results

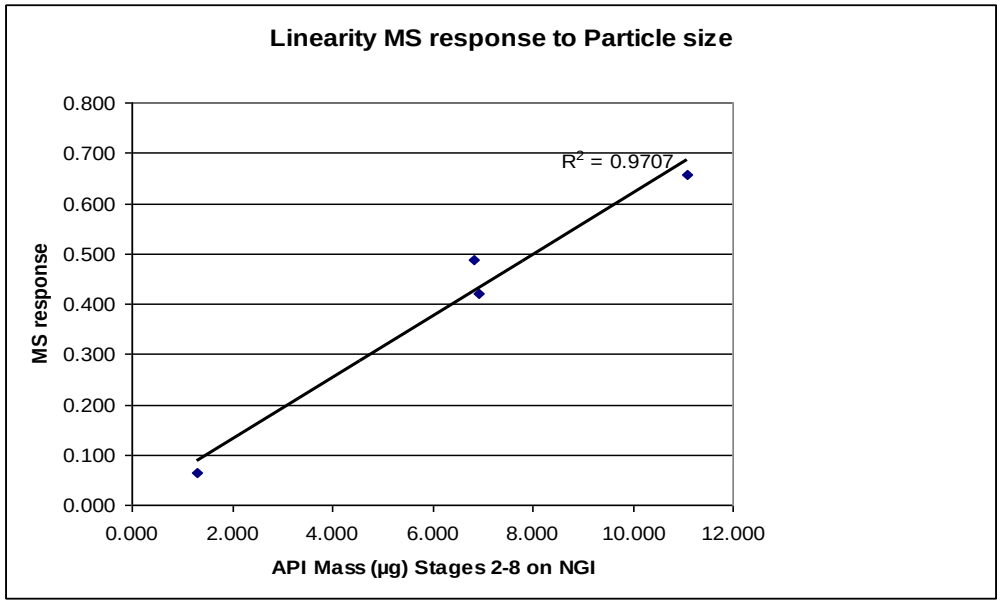
- Reproducibility
  - Better than 10%
  - Linearity (pMDI containing budesonide @ 40/80/160 µg/act)



POTENTIAL FOR A QUANTITATIVE TECHNIQUE EXISTS

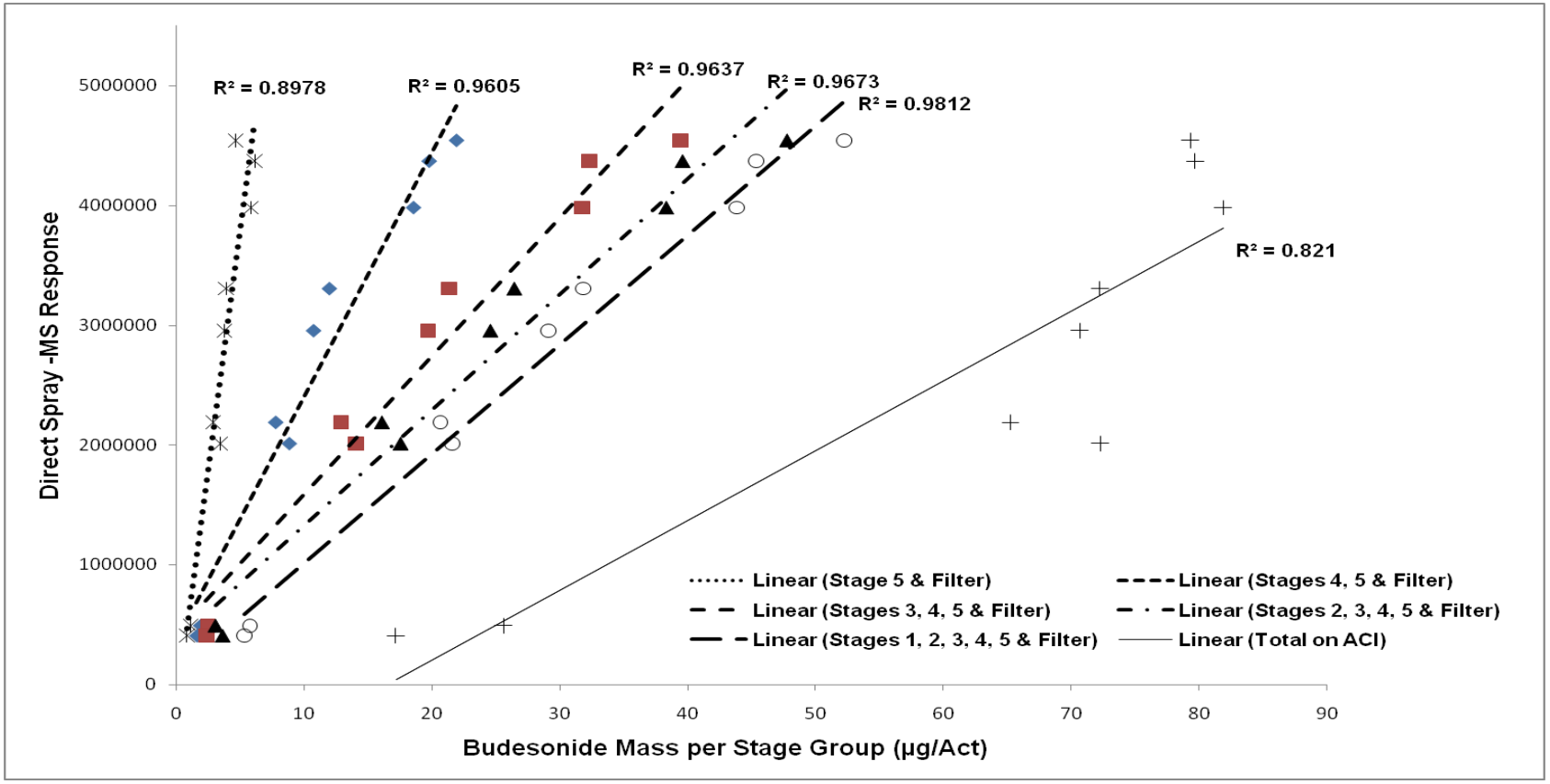
Sensitivity to Particle Size

- The MS has shown a degree of proportionality to large differences in particle size
- Analysing prepared pMDIs with differing particle size material and comparing direct spray response with with NGI mass per stage data (stages 2-8)
  - Linear response indicated



Sensitivity to Sample Size (cont)

Sample Name	D10 (um)	D50 (um)	D90 (um)
Unmicronised Budesonide	41.92	162.14	335.788
Ball milled Budesonide – 600rpm 30 min	0.8435	7.484	63.926
Micronised Budesonide; Setting A	0.652	3.905	11.9245
Micronised Budesonide; Setting B	0.5655	2.9805	8.581



What is it Measuring?

- Optimise Mass Spectrometer test equipment for direct analysis of pMDI, DPI and nebulisers
  - Optimise sample induction techniques
    - Development of Standard induction methods
  - Understand/Optimise airflow into the Spray Chamber
  - Minimise impaction effects/losses
  - Lead to Hardware optimisation?
- Assess the capability of the technique to become a fully quantitative analytical technique for pMDIs
- Evaluate technique for assessment of Fine Particle Dose
- Suitable for any ionisable species

An analytical tool to aid Reduction in pMDI development cycle times

Summary

- The drive to improve analysis efficiency has led to a new focus on seeking alternative approaches to full impactor testing
- AIM initiative is a key activity
  - Faster anaylsis
  - Better decision making (QbD)
  - HRT Relevant measurements (IVIVC)?
    - Other approaches may be as effective
    - Caution when using impactor data in this way
- The search for non-impactor based screening tools continues!
  - Direct Spray-MS continues to show promise (particularly for pMDI)

Acknowledgements

- EPAG Impactor Group – especially Jolyon Mitchell Trudell Medical International for kindly allowing me to use IPAC-RS AIM presentation material

- DDL21 Pre-Conference AIM Workshop December 8th 2010

Thank You

Questions?

Estimating the size of particles reaching the lung