Current Issues in Cascade Impaction

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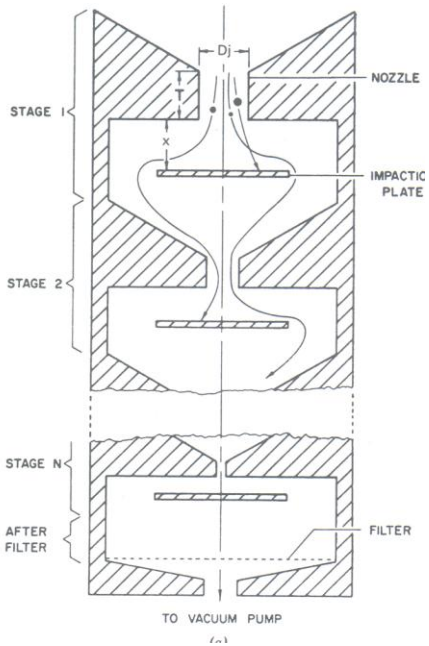
JPAG Meeting

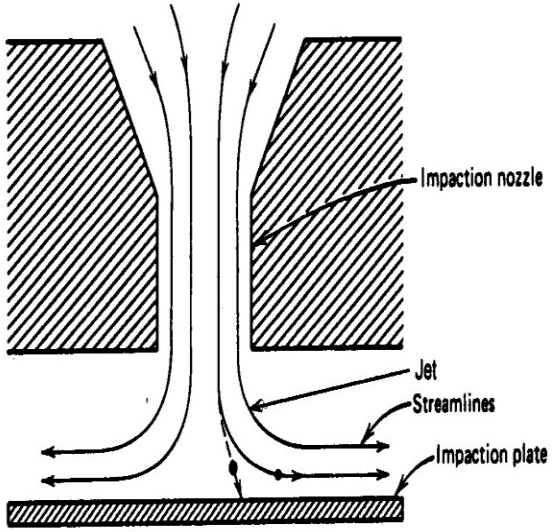
15th October 2009

AstraZeneca
life inspiring ideas

Key Factors

- Impactor Control
  - Coating
  - Leak testing
  - Mensuration
- Method Control Strategies
  - Analytical methodologies
  - Device handling
  - Efficiency
- New Developments
  - Abbreviated Impactor Measurements (AIM)
  - Alternatives to cascade impaction?





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The Hardware

Andersen (ACI)

Next Generation Impactor (NGI)

Marple/Miller

Multi Stage Liquid Impinger (MLSI)

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Andersen Cascade Impactor (ACI)

- Industry Standard for a long time
- Robust and Compact
- Performance well understood
- Full classification of respirable fraction possible
- "Automatable"
- Origins lay in environmental science
- Tricky to Wash down
- *In-situ* sample prep impossible
- Inter-stage losses can be high
- A high degree of skill, including manual dexterity is required to obtain consistent results - (Christopher, D., *et al*. (2003), *J. Aerosol Med.,* 16:235-247)

Next Generation Impactor (NGI)

First Impactor designed specifically for Pharma industry

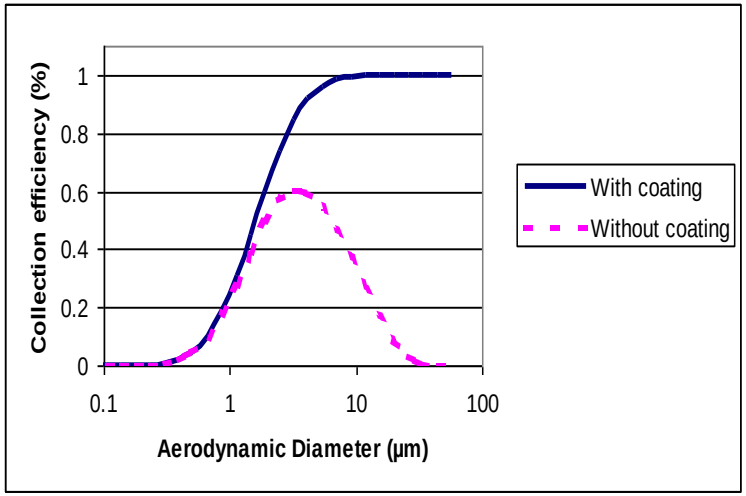
courtesy MSP Corp.

- Bulky (Base unit Heavy)
- Flow resistance
- Some initial Quality Issues
  - Corrosion/jet occlusion
- Serviceability

- Full classification of respirable fraction
- Automation in mind
- **Low inter-stage losses**
- **In-situ sample prep possible**
- ***Faster turnaround*** (however **labour-intensive** cf laser diffractometry time of flight Systems)

Plate Coating

- Impactor Collection Surface Coating (DDL14)
  - Highlighted the range of coating practices in use
  - Range of coating materials
  - Opportunity to Standardise?- Yes??
    - Re-validation could be a barrier to this
  - Provided a ready reference to the range of practices and materials in use
- Cleaning Best Practices (Survey – DDL17)



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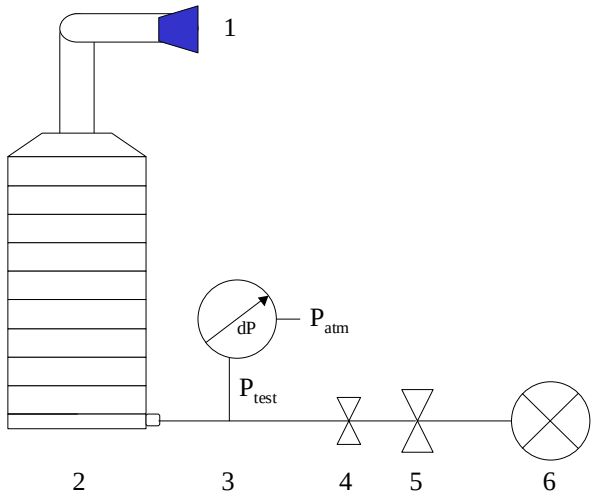
Impactor Leak testing (EPAG Study)

Impactor type	Operational flow	Mole flow* at 1% of operational flow	Internal impactor volume according to [3]	Corresponding leak rate*
NGI with UIP	15 L/min	0.0062 moles/min	1245 mL	12 kPa/min
NGI with UIP + pre-separator	30 L/min	0.0125 moles/min	2025 mL	15 kPa/min
ACI with UIP	28.3 L/min	0.0118 moles/min	975 mL	29 kPa/min
ACI with UIP + pre-separator	30 L/min	0.0125 moles/min	1155 mL	26 kPa/min

*at ambient conditions: T=293.15 K (=20°C), p=101.3 kPa (=atmospheric pressure).

- A new method devised to measure impactor leakage
- DDL18 – Poster made recommendations regarding criteria for a suitable in-use leak test



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Impactor Qualification/Mensuration

- Mensuration of Impactor jet diameters
  - Optical measuring systems typically used
- Most commonly used method for determining CI “fitness for purpose”
- Pharmacopoeial Guidance focuses on achievable manufacturing tolerances
  - Alternative limits can be justified on a case by case basis
- **Can we establish appropriate limits by understanding the capabilities of our measuring systems?**

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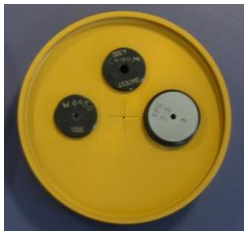
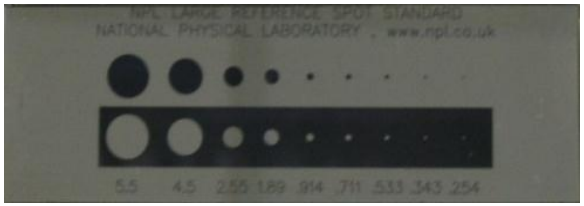
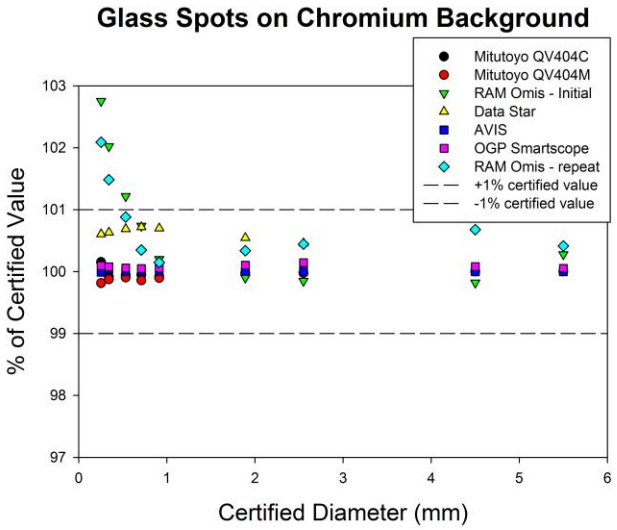
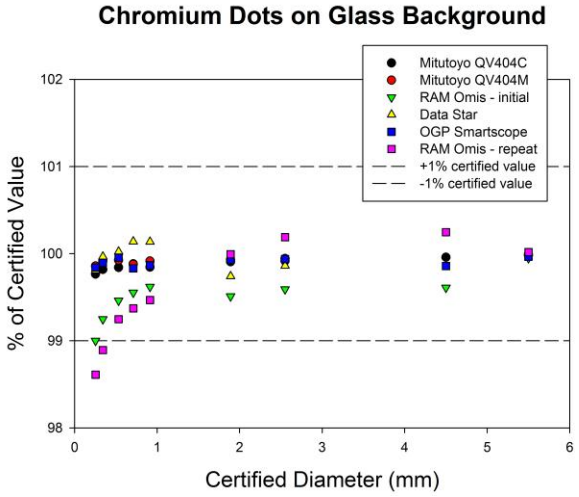
Impactor Mensuration (EPAG Study)

- Accuracy Assessment (6 Sites)
- Calibrated Reticles Ex. Copley
  - Chrome and Glass spot reticles (0.254 - 5.5 mm)
- Ring gauges ex. Westech 1.0, 2.5 & 4.5 mm
- Chrome spots better than 1% @ 0.254mm
- Glass Spots worst case >2% @ 0.254mm
- Ring Gauges all within 1% of Certified values
- Findings submitted to PharmSciTechnol Rev.









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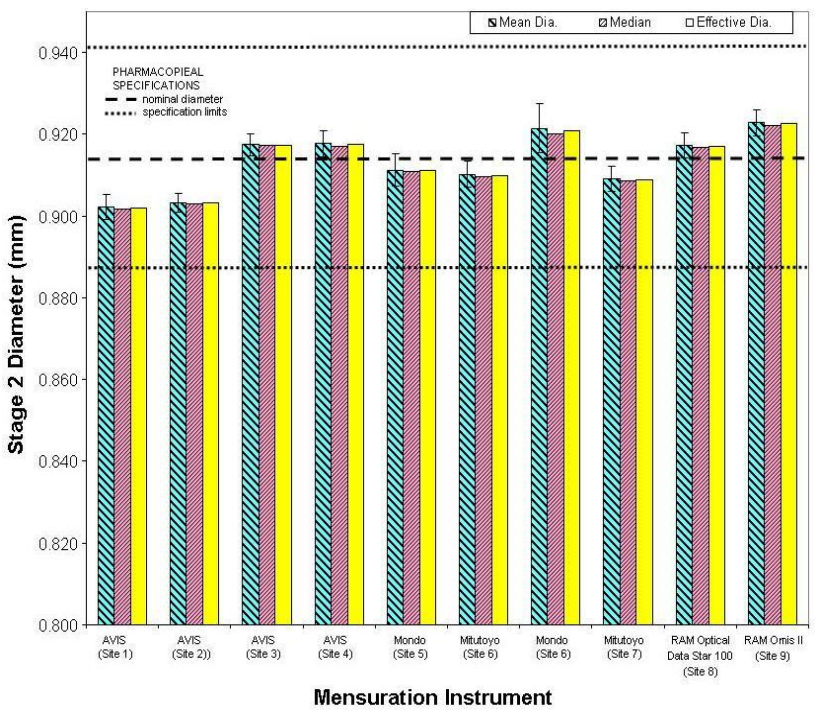
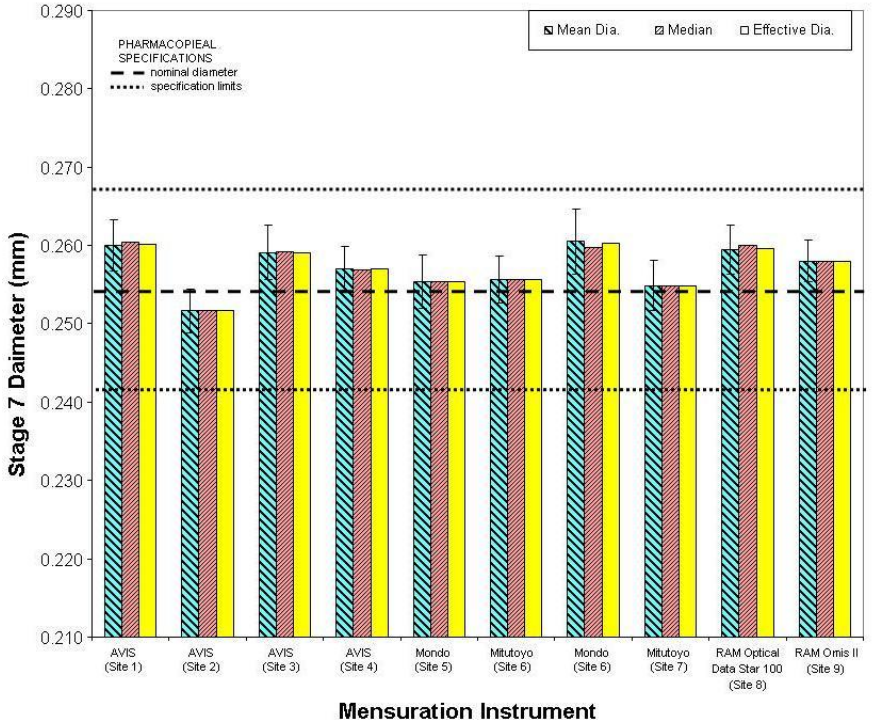
Impactor Mensuration (EPAG Study)

- Precision Assessment (9 Sites)
  - Two ACI Stages (2 & 7)
  - Five Measurement systems evaluated (AVIS/Mituoyo/RAM Omnis/RAM Data Star/Mondo)
  - Good Reproducibility of measurement across sites





Method Control Strategies

Minimising Variability of Cascade Impaction Measurements in Inhalers and Nebulizers

Bonam, Christopher et al for IPAC-RS; AAPS PharmSciTech, Vol 9, No. 2, June 2008

"*The results illustrate the intricate network of underlying causes of CI variability with the potential for several multi-way statistical interactions. It was also found that significantly more quantitative information exists about impactor related causes than about operator-derived influences, the contribution of drug assay methodology and product related causes , suggesting a need for further research in those areas*"

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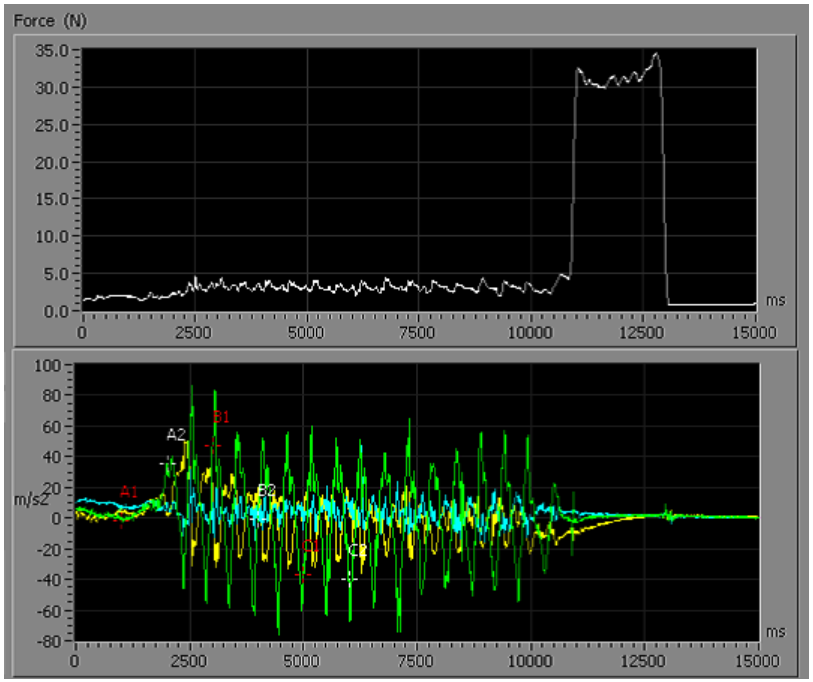
Method Control Strategies

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

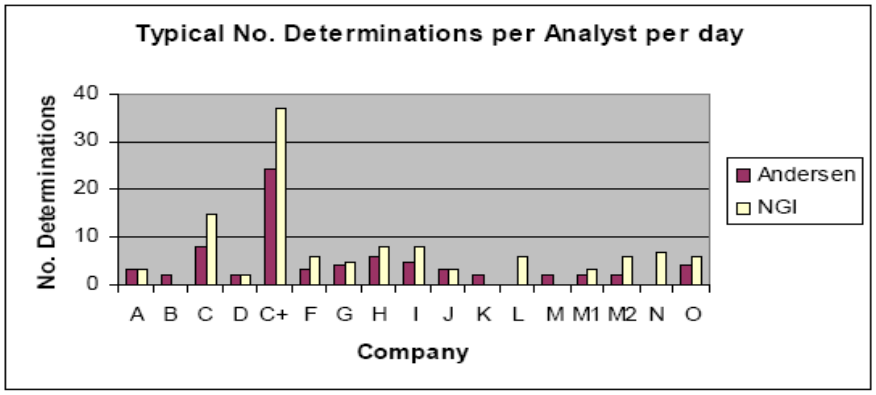
  - Appropriate Analytical test method validation/SST's
    - API recovery from impactor (mass balance checks/re-wash Strategies)
  - Standardized device handling
    - Shake/Fire for pMDI
    - Continued training and monitoring is also important for OINDPs
  - Product specific issues
    - Direct impact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



Measurement of Operator shake/fire inputs

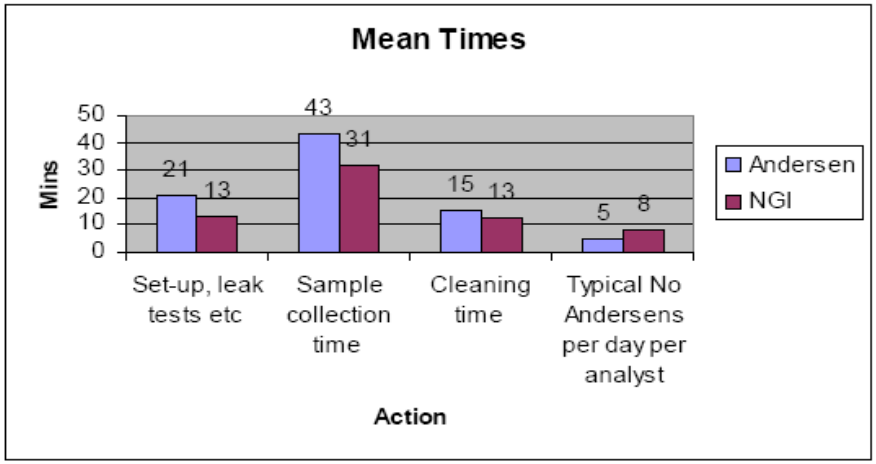
Analysis Efficiency – NGI vs ACI

TYPICAL No. PER ANALYST PER DAY



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

MEANS



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

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New Developments

- Abbreviated Impactor Measurements (AIM)
  - A simplified Impactor based approach to the problem of inhaler Aerosol Particle Size Characterisation
- Alternatives to Cascade Impaction?

Background - AIM

- Assessment of particle size distribution from oral inhaled products (OIPs) is typically by multi-stage cascade impactor (CI)
- Gold standard method:
  - Provides *aerodynamic* size
  - Traceability to drug mass
  - 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*]

AIM is a concept and various impactor tools are available to us

- Essentially modification of existing systems

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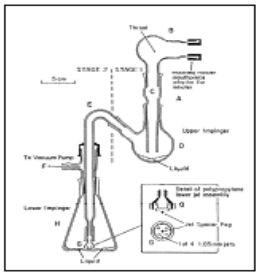
Examples of AIM Systems

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

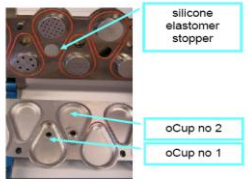
Courtesy Copley Scientific

Courtesy MSP Corp.

Reduced NGI (R-NGI)

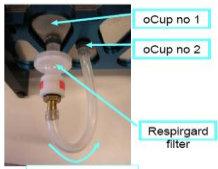
- Use of two oCups is convienient
- Place them after each other on suitable stage positions
- Place a filter after oCup no 1
- Don't forget to plug the normal air passage

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

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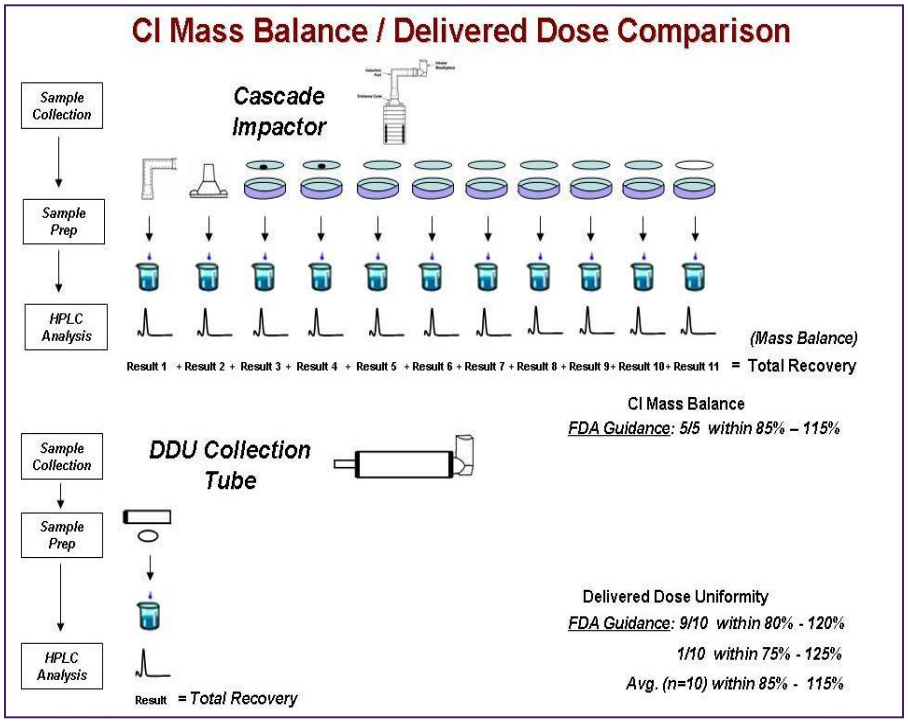
Full Resolution CI Measurements

- 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



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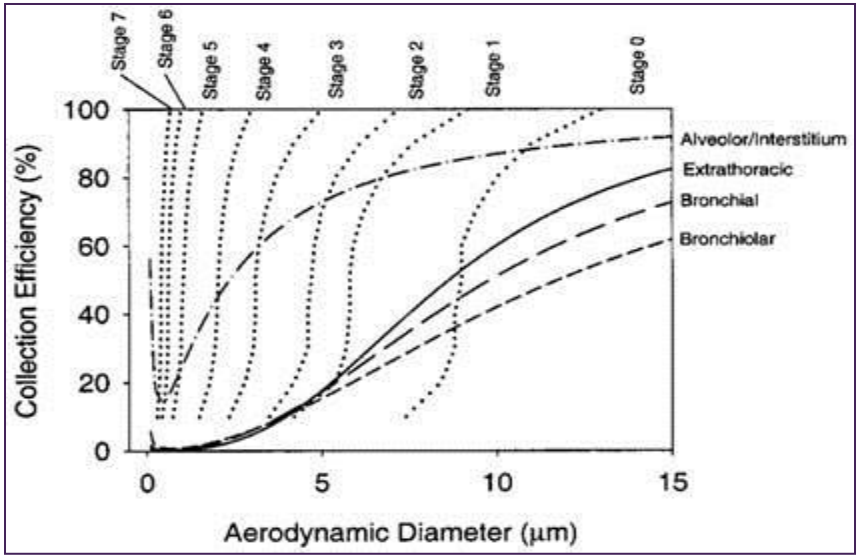
CI STAGE RESOLUTION IN RELATION TO PARTICLE DEPOSITION PROCESSES

- **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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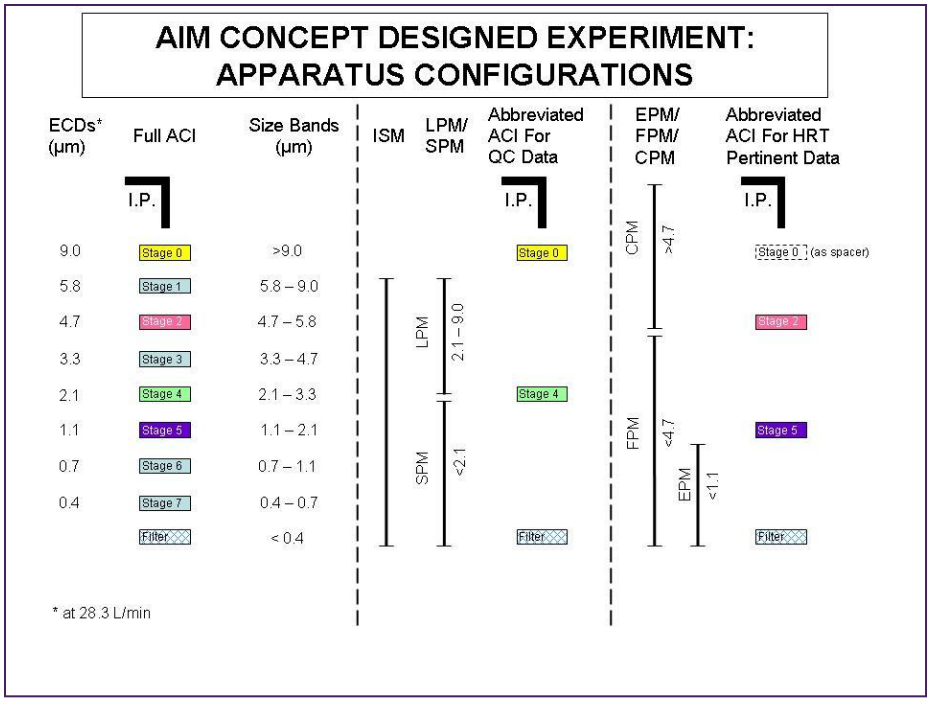
Why Consider AIM Systems?

- Faster Analysis
  - 3 – 4 stage measurement cf ~ 9 - 11 stage determinations
- Flexibility
  - Tailor stage selection to the parameters required
    - QC or Human Respiratory tract pertinent measurement
  - Robust to flow rate



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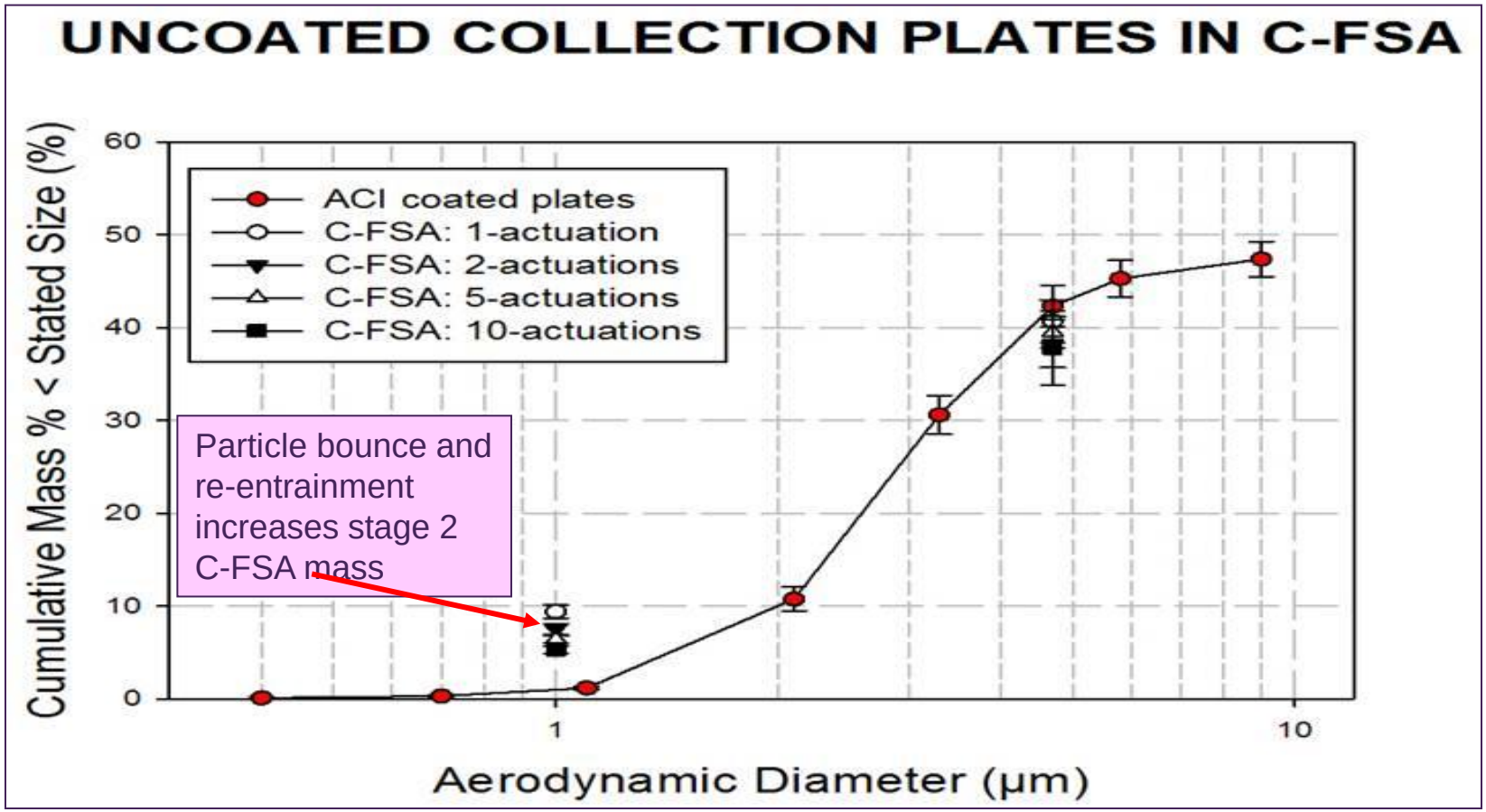
Coating of collection plates for ACI and C-FSA is *essential* for the most accurate work



A Brij-soaked glass microfibre filter on stage 2 can reduce bias due to particle bounce

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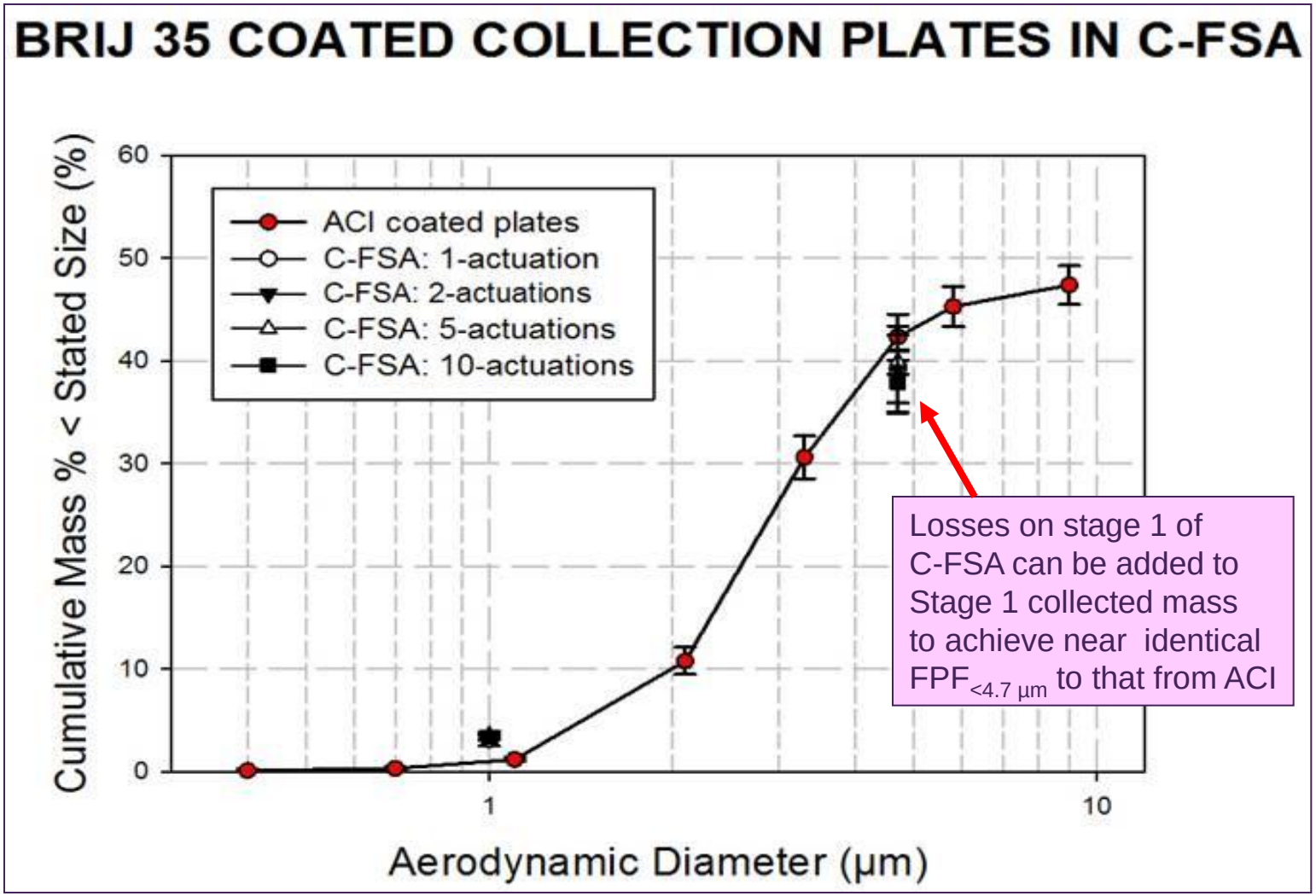
Substantial equivalence has been achieved between C-FSA and ACI



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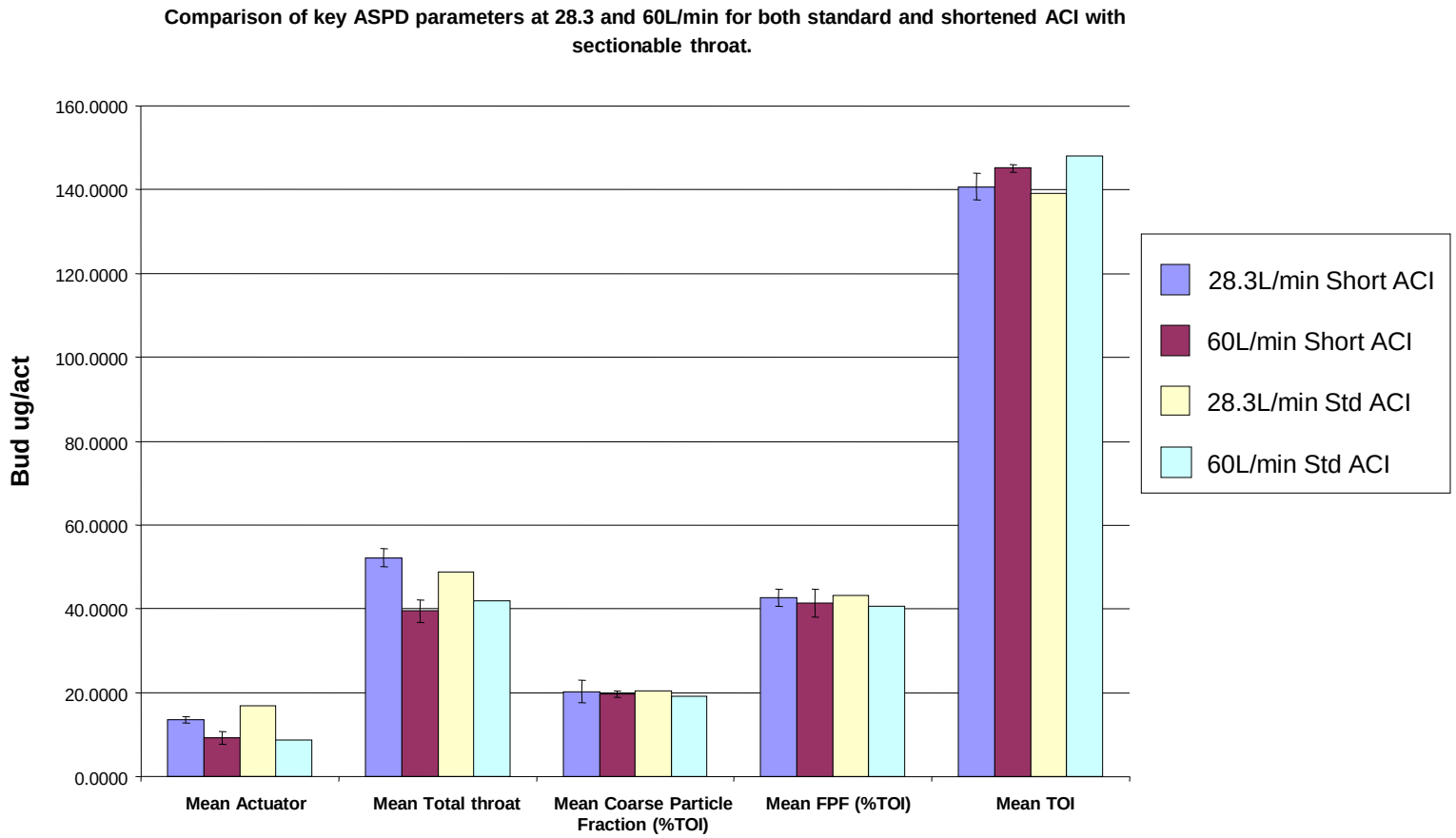
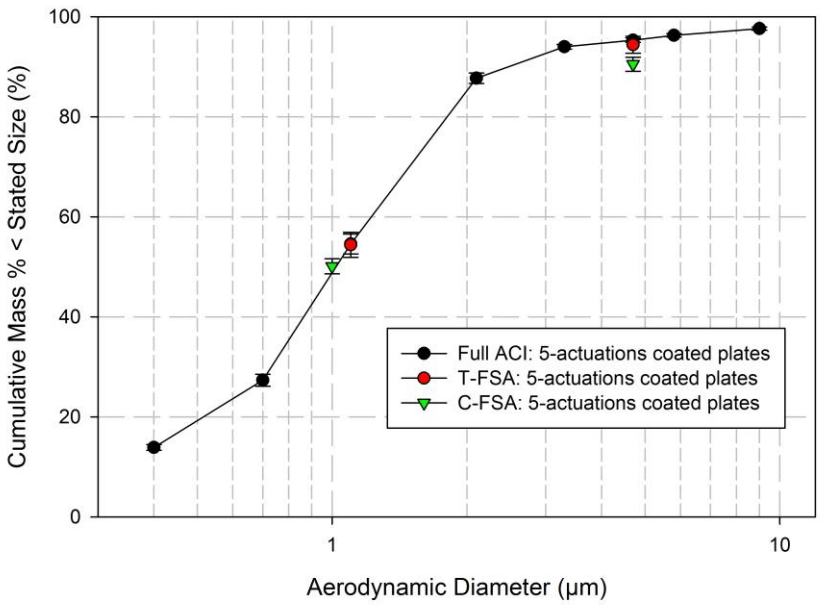
Flow rate effects - Short Stack ACI (AZ)

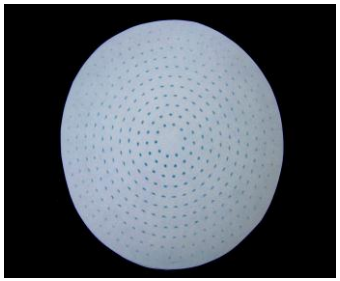
- Stack composition – IP/Stage 0/Stage 2/ stage 7/Filter
- Stage 1 substituted for stage 2 @ 60 Litres min^{-1}

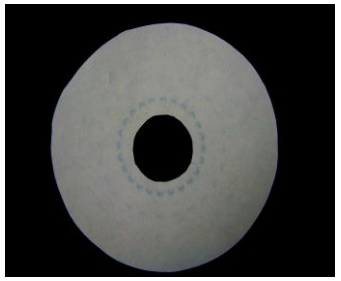


EVAPORATIVE EFFECTS – QVAR*

Fig. 7: Trudell T-FSA vs. Copley C-FSA and Full ACI with Qvar*-100 as Test Formulation - Excluding Mass Collected by Induction Port







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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Non-Impactor Based Systems

Malvern SprayTec
(Laser Diffractometry)

ELPI

TSI Aerodynamic
Particle Sizer (APS)

- Spraytec/APS most applicable to solution based formulations
- ELPI suffers from charge per particle issues and EMF effects
- All the above cannot offer API specific detection
- Current screening techniques like Spraytec/APS/ELPI lack specificity to drug components in the formulation
- Is there an alternative?

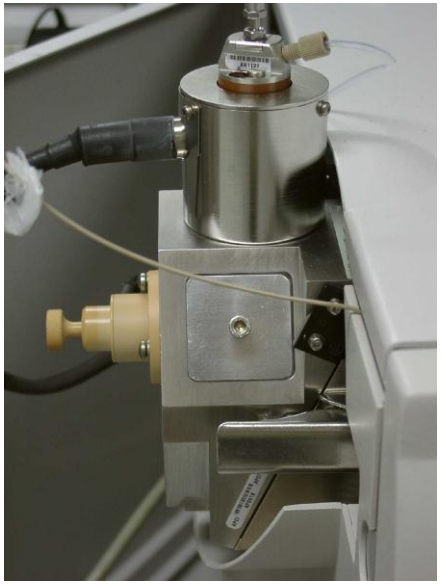
Direct Spray MS (direct sample induction)

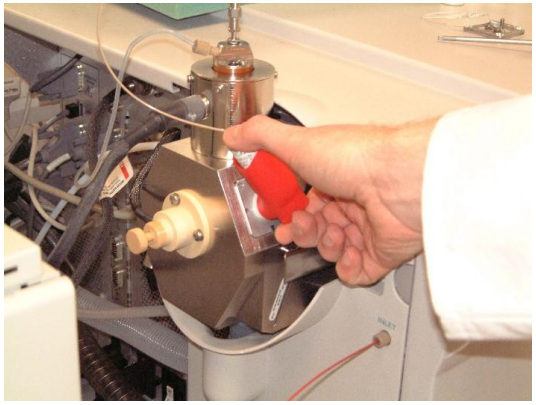
- Current screening techniques like APS/ELPI/Spraytec lack specificity to drug components in the formulation
- Could Mass Spec selectivity offer a solution to these issues?
  - Droplet size range from pMDI similar to that produced by an LC-MS nebuliser spray
  - If so how would we approach it?
  - LC-MS?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

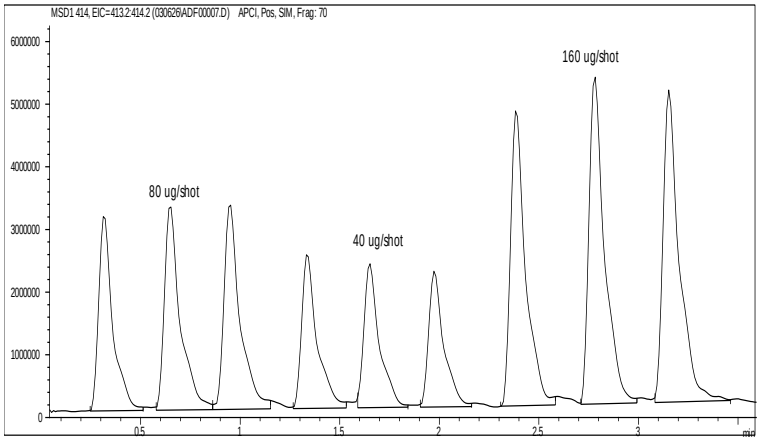
Pat Ref –WO/2008088270

How it works

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

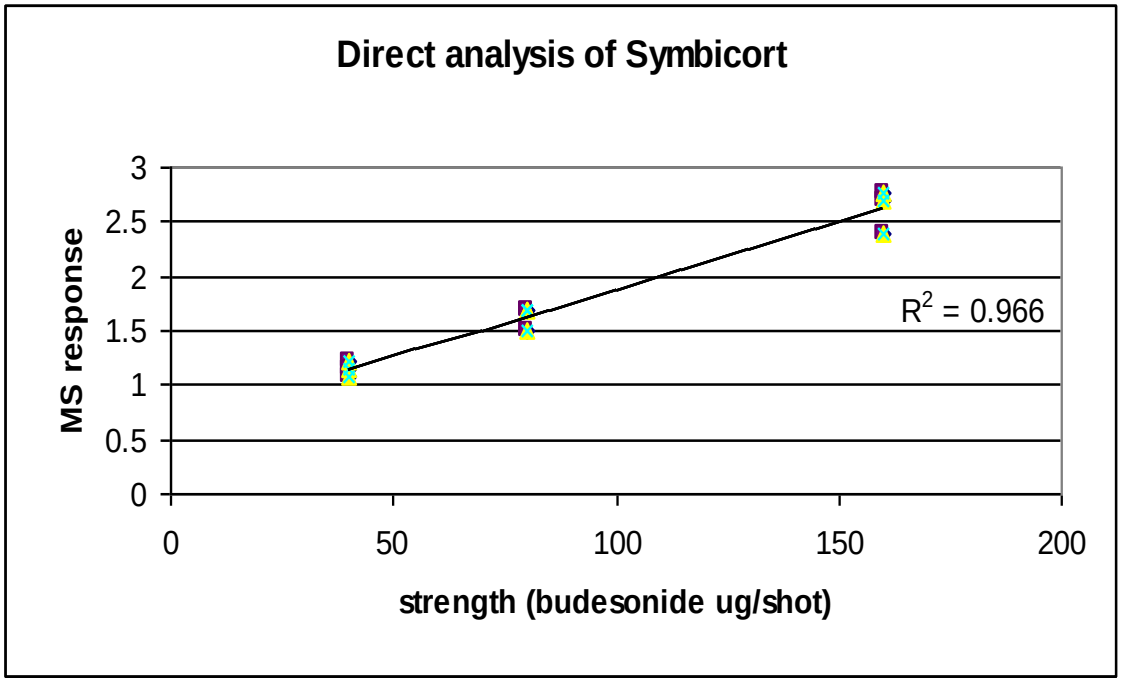






Initial Results

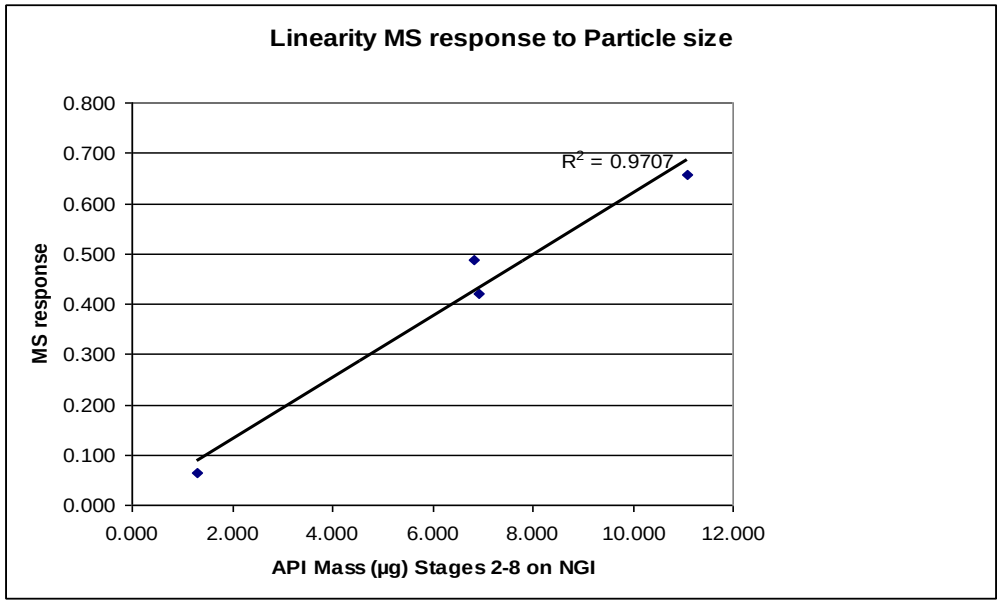
- Reproducibility
  - Better than 10%
  - Linearity - Symbicort 40/4.5, 80/4.5, 160/4.5



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 with good correlation



Future work

- 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
  - The search for no-impactor based screening tools continues!
- Control of impactors in-use is key to minimising
  - Standarised approaches will be an advantage
    - Pharm industry and regulators
  - Product specific issues will remain
    - Method validation and device handling issues need to be considered on a case by case basis

Acknowledgements

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

Questions?