

The Abbreviated Impactor Measurement (AIM) Concept for Aerodynamic Particle Size Distribution (APSD) in a Quality-by-Design (QbD) Environment

Jolyon P. Mitchell Ph.D.

Trudell Medical International
London, Ontario, Canada

IPAC-RS Conference, Bethesda, MD, September 22-24, 2008

1

IPAC-RS 2008 Conference

AIM IS A CONCEPT: NOT A PARTICULAR MEASUREMENT APPARATUS

- Many possibilities exist to determine meaningful aerodynamic size-related metrics in a simplified manner
 - This flexibility is important, given the variety of inhaler classes and formulations

2

IPAC-RS 2008 Conference

THE IMPORTANCE OF APSD FOR INHALER PERFORMANCE

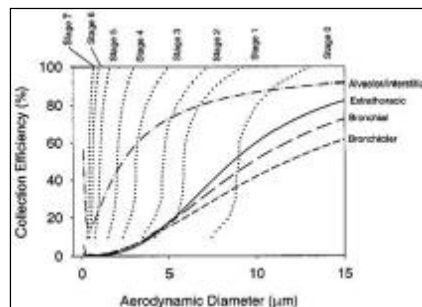
- **APSD is a critical quality attribute of *in vitro* inhaler performance:**
 - Aerodynamic size is related to particle deposition in the respiratory tract
- **The need to acquire a thorough knowledge of APSD is a priority in oral-inhaled product development:**
 - The multi-stage cascade impactor (CI) method provides direct traceability to mass of active pharmaceutical ingredient (API) as a function of aerodynamic diameter

3

IPAC-RS 2008 Conference

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

4

IPAC-RS 2008 Conference

CAPABILITIES OF EXISTING MULTI-STAGE CIs

- **The Andersen 6- and 8-stage designs (ACI), are based on technology intended for ambient air quality assessments**
 - The 8-stage non-viable ACI provides 5 sub-fractions between 0.5 and 5.0 μm aerodynamic diameter
 - deemed important for regulatory purposes in the past
- **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



ACI with Ph.Eur/USP Induction Port

5

IPAC-RS 2008 Conference

NEXT GENERATION PHARMACEUTICAL IMPACTOR (NGI)

- Designed for inhaler testing from the outset:
 - Similar size resolving capability to that of the 8-stage ACI
 - ... but more efficient, especially when semi-automated
 - ... however, **still labor-intensive** compared with laser diffractometry (LD) and time-of-flight (TOF) methods



An open NGI showing collection cups loaded

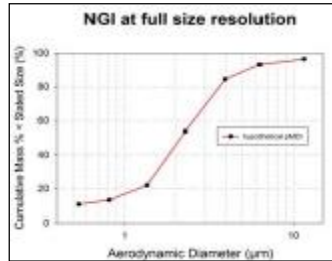
courtesy MSP Corp.

6

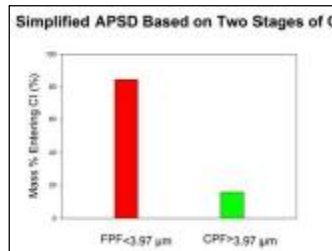
IPAC-RS 2008 Conference

QUESTIONS TO PONDER

1. What are the *critical metrics* for APSD?
2. Is there a need for high size resolution *all of the time*?
3. How can current APSD measurement technology be adapted to a QbD environment?
 - Development
 - Stability testing*
 - Release



OR



*Since stability testing is done for identification of trends/changes, is lower APSD resolution all that is needed?

This is an example scenario – other cut sizes could be adopted 7

WHAT ARE THE CRITICAL METRICS?

- Particles smaller than ca. 5 µm efficiently pass through the upper respiratory tract
- A single size boundary may therefore be sufficient for many *in vitro-in vivo* analyses
- **Full size resolution may therefore not be needed for all APSD measurements:**
 - *i.e.* once the full APSD profile of the product has been established in development

METRIC	
Fine particle fraction [†]	FPF (%)
Coarse particle fraction	CPF (%)
Mass balance as % label claim*	MB

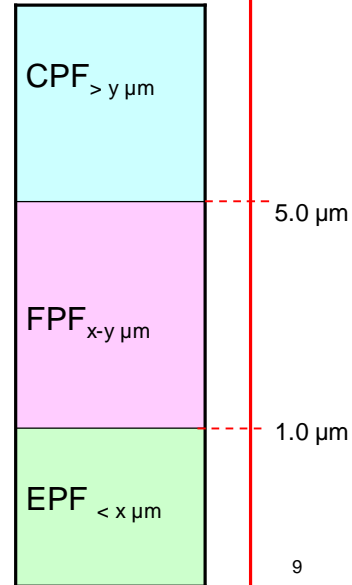
* Includes mass in inhaler actuator, induction port, pre-separator (if used)

[†] may be defined with a lower as well as an upper size limit for the cost of adding an extra stage to the size analyzer

A REFINEMENT

- **FPF could be defined with a lower as well as an upper size limit**

- Precise limits would likely be formulation dependent
- Definition of extra-fine particle fraction (EPF) may be useful for formulations intended for deep lung penetration
- Extra-fine particles may be more likely to be exhaled before depositing in the HRT



IPAC-RS 2008 Conference

CPF AND (TOTAL) DELIVERED MASS

- **CPF determination will likely involve the pre-separator, especially if inhaler is a DPI:**

- Pre-separators are typically bulky
- Time-consuming to recover deposited API

- **If further sub-division into CPF/FPF/EPF is not required:**

- Delivered (mass) dose (DD) from a DDU apparatus may be an attractive alternative to determination of DD by abbreviated or full CI

10

IPAC-RS 2008 Conference

AIM: 4-WAYS TO CONSIDER

1. Liquid impingement
2. ACI-derived options
3. NGI-derived options
4. Semi or full automation

11

IPAC-RS 2008 Conference

1. LIQUID IMPINGEMENT

- The compendia have moved away from liquid impingement, especially the Twin Impinger (TI), in recent years:
 - Insufficient size resolution
 - Should this paradigm be re-visited as part of the AIM concept?
- The full MSLI is the only impingement-based apparatus currently recognized in the *Ph. Eur.*
 - Semi/fully-automated multi-stage liquid impinger (MSLI) systems are possible

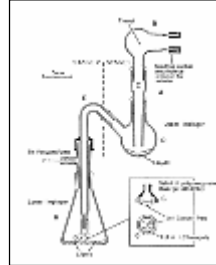
12

IPAC-RS 2008 Conference

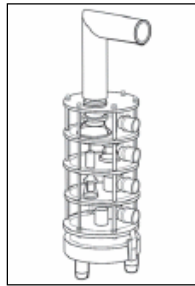
LIQUID IMPINGEMENT (LI)

- Advantages:**

- API can be collected directly in eluent for assay
- More API mass may be collected without overloading



Does the Twin-Impinger (TI) have a role to play?



Is there scope for a reduced Multi-stage Liquid Impinger (MSLI)?

Liquid impingement options

13

IPAC-RS 2008 Conference

2. ACI-DERIVED OPTIONS



Courtesy Westech Instruments Inc.

Westech Short-Stack Fine Particle Dose (FPD) impactor: based on the viable ACI with Petri dish sample collection



Courtesy Copley Scientific

Copley Short-Stack Fast Screening Andersen Impactor (C-FSA): based on the non-viable ACI using standard collection plates

14

IPAC-RS 2008 Conference

3. NGI-DERIVED OPTIONS

- The NGI was originally intended as a full resolution CI
- However, the possibility of utilizing deep cups to 'switch off' selected stages would provide an alternate pathway without the need to acquire another CI design



Courtesy
MSP Corp.

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

Theoretical work already undertaken at MSP Corp. based on the experimental methodology for the archival calibration has demonstrated the potential of this simple approach

15

FAST SCREENING IMPACTOR (FSI)

- Based on a modified NGI pre-separator with cut-point at 5 μm aerodynamic diameter
- Aerodynamic size fractionation in pre-separator is excellent because of 2-stage design*
- Flow rate range is from 30 L/min to 100 L/min in 5 L/min increments
- Other flow rates could be readily accommodated



Courtesy MSP Corp.

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

16

REDUCED NGI (R-NGI)

- AstraZeneca modified outlet collection cups: **The 'O'-cup approach**
 - uses existing design but takes particles leaving desired fractionation stage direct to filter
- Stage 1 orifice diameter of NGI adjusted by inserts to achieve nominal cut-point at 5 μm aerodynamic diameter at several defined flow rates
 - useful for cases where fine and extra-fine fractions need to be distinguished by having stage 6 also operational



Courtesy MSP Corp.

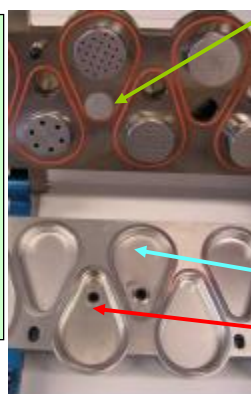
Vented 'o'-cup is an alternative to the deep-cup option

17

IPAC-RS 2008 Conference

DETERMINATION OF FPD BY NGI WITH 'o-CUP': PRACTICAL CONSIDERATIONS

- Use of two oCups is convenient
- Place them after each other on suitable stage positions
- Place a filter after oCup # 1
- Don't forget to block the normal air passage



silicone elastomer stopper

oCup no 2

oCup no 1

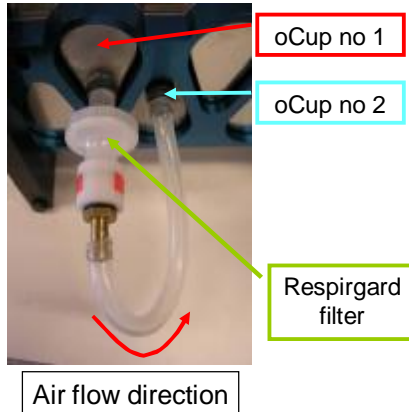
Courtesy Mårten Svensson, AZ Lund

18

IPAC-RS 2008 Conference

'o-CUP' – VIEW BENEATH NGI

- 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 Svensson, AZ Lund

4. SEMI OR FULL AUTOMATION BASED ON SINGLE-STAGE ACI COMPONENTS



AstraZeneca Fully-Automated Single Cut-Off Stage Impactor (SSI)
(see Lundbäck and Wiktorsson RDD-2006; 467-470 for semi-automated version)



Courtesy Hans Lundbäck
AstraZeneca Lund

PROOF OF AIM CONCEPT: VALIDATION OF C-FSA

- Program of work at Trudell Medical International to evaluate the AIM approach:
 - **'Proof-of-concept' experiments**, focusing initially on the C-FSA
 - **Identify potential causes of non-ideal behavior**
 - Utilizes standard ACI-measurements as the reference data

Courtesy
Copley
Scientific



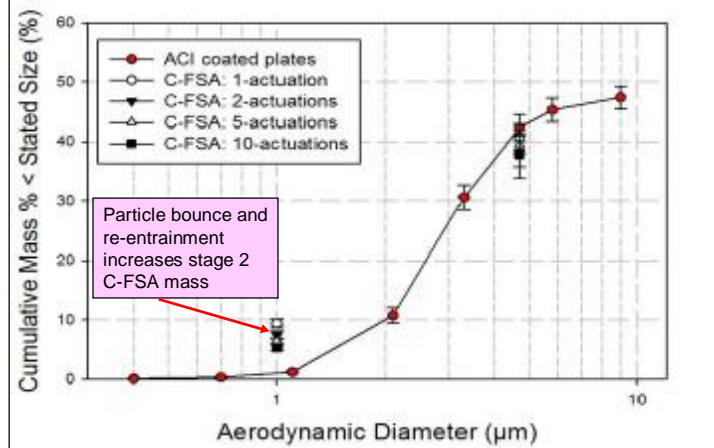
Copley Short-Stack Fast Screening Andersen Impactor (C-FSA) used in TMI studies

21

IPAC-RS 2008 Conference

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

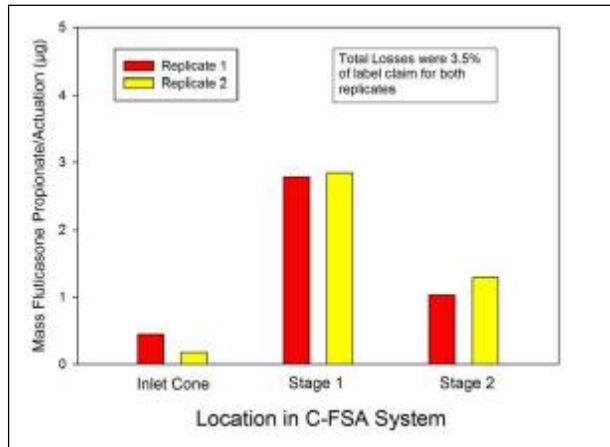
UNCOATED COLLECTION PLATES IN C-FSA



22

IPAC-RS 2008 Conference

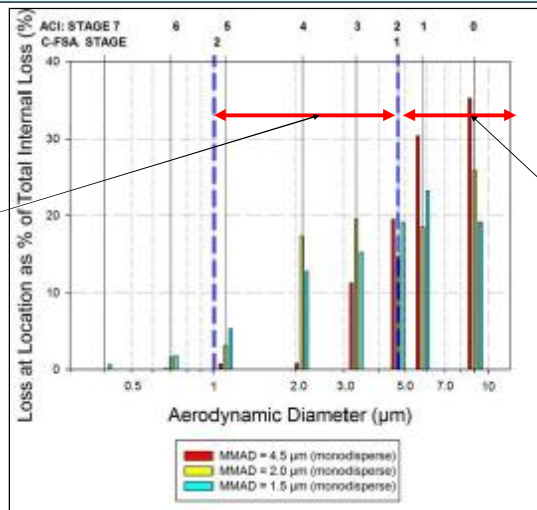
Internal losses in the C-FSA are < 5% label claim with coated plates



23

IPAC-RS 2008 Conference

Re-located internal losses in ACI when converted to C-FSA account for small discrepancies between methods



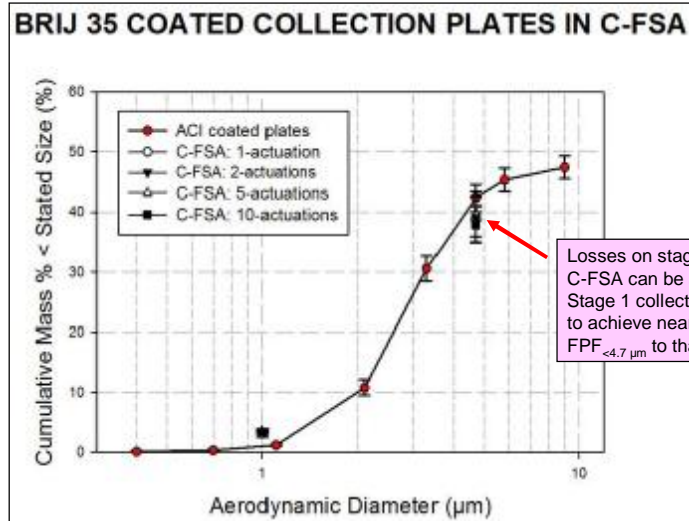
Internal losses for missing ACI stages 3-4 transfer to C-FSA stage 2

Induction Port removes almost all particles >5 µm

24

IPAC-RS 2008 Conference

Substantial equivalence has been achieved between C-FSA and ACI



25

IPAC-RS 2008 Conference

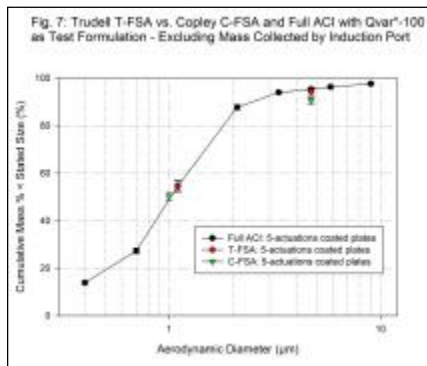
NEXT STEP: ASSESS EVAPORATIVE EFFECTS FOR LOW VOLATILE EXCIPIENTS

- Evaluate if evaporative effects are significant:
 - Initially with a solution pMDI formulation containing ethanol, such as Qvar*
 - Extend AIM to aqueous solutions for nebulization
- The R-NGI may be less prone than the C-FSA to such effects as its internal open space will be quite similar to that of the standard NGI configuration

26

IPAC-RS 2008 Conference

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

27

IPAC-RS 2008 Conference

AIM-RELATED QUESTIONS

28

IPAC-RS 2008 Conference

1. What is the most useful cut-point size for fine/coarse particles?

- Does 5.0 μm aerodynamic diameter as specified in 2.9.18 of the Ph. Eur. make sense as a universal standard?

- stage 2 of the ACI at 28.3 L/min is 4.7 μm and <601> of the USP does not specify a precise value?

- What about a QbD approach, in which the cut-point size selection is made based on knowledge of the product size properties?

- Method precision can be optimized by choosing a value that is close to the MMAD
- Likely to be of limited value for FPF/CPF boundary size selection, but may be appropriate for EPF/FPF boundary with some formulations, such as many solution-pMDIs

29

IPAC-RS 2008 Conference

2. What about developing AIM-instruments with cut-point size that is inhaler-appropriate?

- Comparatively easy to do, depending on option chosen
- Would take into account effect of DPI resistance on flow rate at which APSD is measured by compendial method
- Avoids need for data interpolation with assay values going directly to LIMS to calculate EPF/FPF/CPF
- Could be especially useful in a PAT environment

30

IPAC-RS 2008 Conference

3. What in terms of fine particle mass should be submitted when AIM is deemed appropriate?

- Mass < 4.7 μm or < 5.0 μm ?
- Mass between 1.1 and 4.7 μm ?
- No fixed limits, being product /quality driven?
- Other?

4. Is there any need for size distribution moments (i.e. MMAD, GSD) all the time?

- Such data requiring a full APSD may not be necessary for routine measurements

31

IPAC-RS 2008 Conference

NEXT STEPS

- **Establish the value of the AIM concept with input from industry, regulators and academia:**
 - What are the CQAs we should be measuring ON A ROUTINE BASIS?
 - What can AIM offer and where?
 - Can EPF/FPF/CPF from AIM be used with DDU in quality control as the tool of choice for monitoring trends in EPM/FPM/CPM?
 - What other attributes of reduced measurement systems are seen as important?
 - How should AIM be treated in the compendia?
- **Encourage as wide a debate as possible over the next year or two, with the prospect of developing AIM to the point at which it can become widely applied**
- I will act as a focal point for idea sharing within the context of the IPAC-RS CI WG and EPAG CI Sub-Team

32

IPAC-RS 2008 Conference

TWO FINAL THOUGHTS

- Careful application of the AIM concept should result in more efficient APSD measurements during both product development and quality control testing whilst still maintaining method robustness
- The precision of AIM-determined metrics should be better compared with precision from full CI-based data where many stages collect almost no API
- The AIM concept would not eliminate the requirement for complete APSD profiles, especially in early stage product development, but such data might only be needed to establish and confirm the product profile is both reproducible and stable

33

IPAC-RS 2008 Conference



ACKNOWLEDGEMENTS:

to Mark Nagel and my colleagues at **Trudell Medical International**, Mark Copley (**Copley Scientific Ltd**)
Daryl Roberts (**MSP Corp**), Mårten Svensson (**AstraZeneca**),
and colleagues within both the European Pharmaceutical
Aerosol Group (**EPAG**) and **IPAC-RS** for advice
during the preparation of this presentation

August 2008