

Precision and Accuracy of AIM / EDA

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Designed Experiment

- Study designed by IPAC-RS Cascade Impactor Working Group
- Study performed by Aerosol Laboratory of Trudell Medical International, London, Ontario, Canada

General Considerations

- **Efficient Data Analysis (EDA) approach**
 - More effective decision tool for detecting shifts in APSD
 - Can be combined with Abbreviated Impactor Measurement (AIM) for more efficiency
- **Need to compare precision and accuracy of EDA approach when used with AIM versus full-resolution impactor system**

Objectives

- **Demonstrate that the precision of both abbreviated impactors is at least as good as the full-resolution impactor**
- **Identify any potential sources of bias in the abbreviated measurements**

Study Design

Six-day study, with 3-analyst team, balanced testing across three different impactor systems

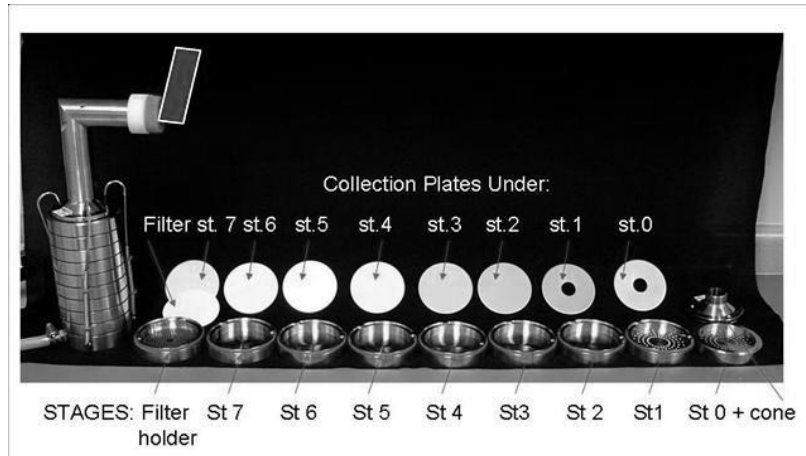
- Full-resolution 8-stage Andersen cascade impactor (ACI)
- Abbreviated impactor for Quality Control (QC) metric
- Abbreviated impactor system for Human Respiratory Tract (HRT) metric

Experiment Design

Inhaler (Test Occasion)	Sequence Replicate	Dosing Set for Each CI			CI Order within Replicate
		ACI	QC	HRT	
1	1	1	2	3	ACI QC HRT
	2	5	6	4	HRT ACI QC
	3	9	7	8	QC HRT ACI
2	1	2	1	3	QC ACI HRT
	2	4	6	5	ACI HRT QC
	3	9	8	7	HRT QC ACI
3	1	1	3	2	ACI HRT QC
	2	6	5	4	HRT QC ACI
	3	8	7	9	QC ACI HRT
4	1	3	1	2	QC HRT ACI
	2	5	6	4	HRT ACI QC
	3	7	8	9	ACI QC HRT
5	1	1	3	2	ACI HRT QC
	2	5	4	6	QC ACI HRT
	3	9	8	7	HRT QC ACI
6	1	2	3	1	HRT ACI QC
	2	4	5	6	ACI QC HRT
	3	9	7	8	QC HRT ACI

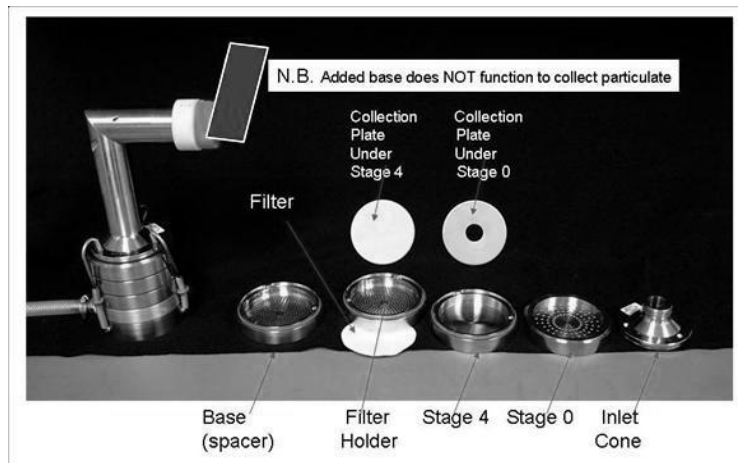
- Tightly controlled ambient temperature and humidity
 - $T_{amb} = 21.0 \pm 1.0^{\circ}\text{C}$
 - $RH_{amb} = 45 \pm 5\%$
- HFA-albuterol (blinded product)
 - Intentionally selected for smallest product variability
 - to enhance ability to detect any signals from the method
 - Using sequential canisters from the same portion of the manufacturing run (~1 minute worth of production)

ACI Configuration



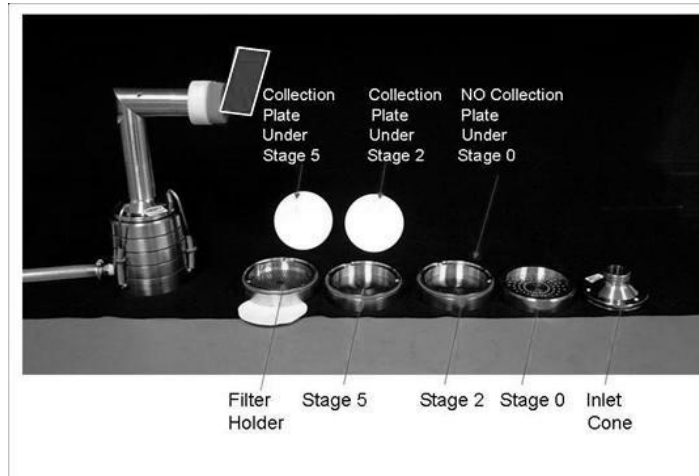
Configuration of full resolution ACI (benchmark system)

QC Configuration (AIM)



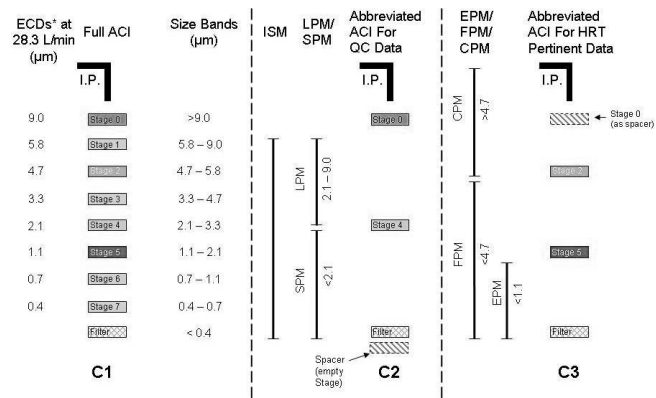
Configuration of quality control metric (QC) abbreviated system

HRT Configuration



Configuration of human respiratory tract metric (HRT) abbreviated system

Comparison of Configurations

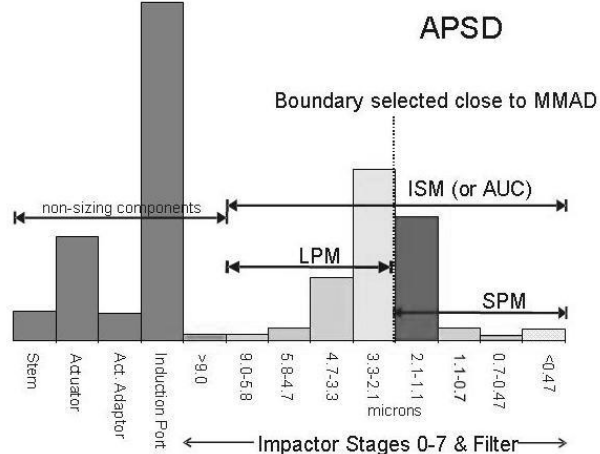


Impactor configurations used in the experiment

Data Analysis

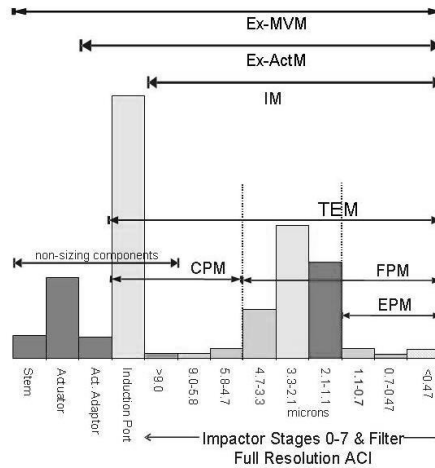
- **Statistical analysis was conducted to estimate and compare the repeatability of three CI configurations side-by-side, based on first quantifying the following three principal metrics related to the total mass of albuterol emitted from the inhaler, normalized per-actuation:**
 - **impactor mass (IM),**
 - **ex-actuator mass (Ex-ActM),**
 - **ex-metering valve mass (Ex-MVM).**

Measured Quantities (1)



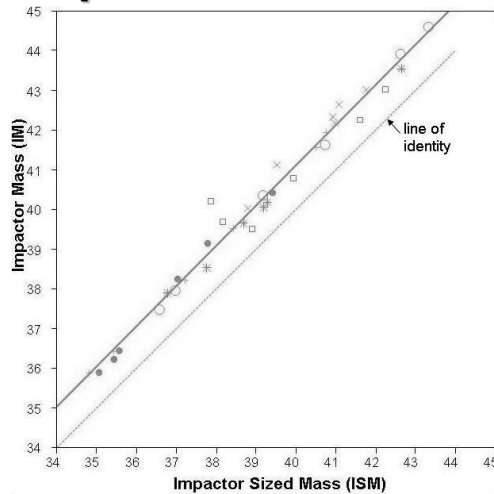
Relationship between measured quantities for the QC and ACI configurations.

Measured Quantities (2)



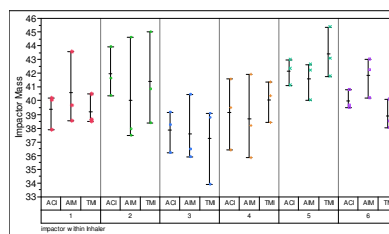
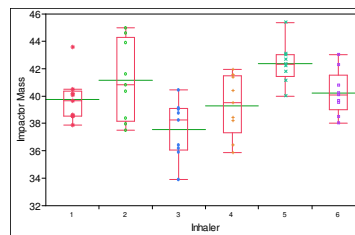
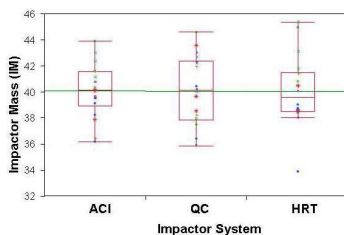
Relationship between measured quantities for the QC and ACI configurations.

Comparison of Impactor Mass and Impactor Sized Mass



Relationship between IM versus ISM, showing measurements with a different symbol for each of the 6 inhalers evaluated

Comparisons of IM

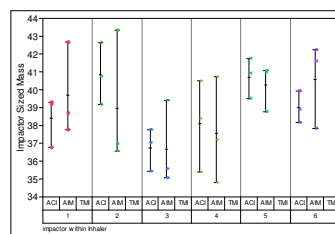
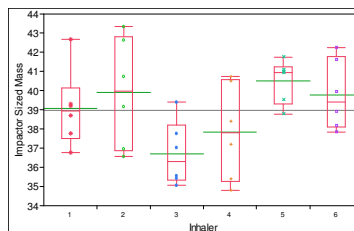
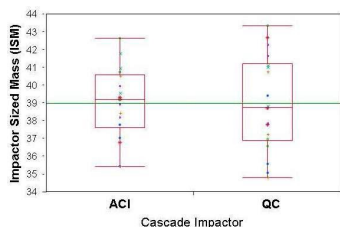


- substantial equivalence in precision
- no pattern related to impactor order in study
- small inter-inhaler differences detected by all systems

Summary Statistics: IM, Ex-ActM, Ex-MVM

Metric	Impactor Configuration	Mean (µg)	Std .Deviation (Repeatability). (µg)	CV (%)	95% confidence interval on ratio of Std. Deviations of abbreviated to full configuration
IM	ACI	40.08	1.60	3.99	-
	QC	40.05	2.66	6.64	[0.92; 3.01]
	HRT	40.03	2.14	5.34	[0.74; 2.42]
Ex-ActM	ACI	79.51	3.35	4.21	-
	QC	79.89	3.48	4.35	[0.56; 1.89]
	HRT	80.19	3.74	4.67	[0.61; 1.96]
Ex-MVM	ACI	96.28	4.22	4.39	-
	QC	96.58	3.91	4.05	[0.57; 1.54]
	HRT	96.75	3.92	4.06	[0.57; 1.55]

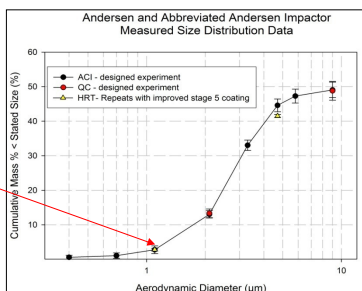
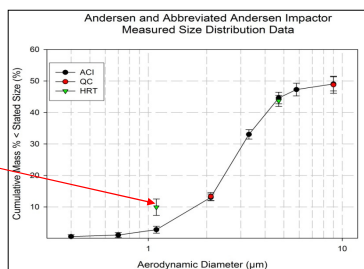
Comparisons of ISM



- similar outcome to IM comparison but restricted to QC abbreviated system

APSD Comparison

- All metrics consistent with full resolution ACI with exception of EPF
- Bias in EPF associated with high inertia particles bouncing on second impaction stage
 - Part 2 of study
 - Bias eliminated by floating a surfactant-saturated filter onto this stage



Assessment of ISM and LPM/SPM

Results

Metric	Impactor Configuration	Mean (µg)	Std .Deviation (Repeatability). (µg)	CV (%)	95% confidence interval on ratio of Std. Deviations of abbreviated to full configuration
ISM	ACI	38.97	1.57	4.07	-
	AIM-QC	38.96	2.68	6.87	[0.93; 3.05]
LPM/SPM	ACI	2.79	0.28	9.98	-
	AIM-QC	2.69	0.35	12.83	[0.68; 2.24]

Acknowledgements

- **Jolyon Mitchell, Mark Nagel and Aerosol Laboratory team, Trudell Medical International**
- **Jorge Quiroz, Merck**

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“2nd Experiment”

2nd Experiment

- Study designed by IPAC-RS Cascade Impactor Working Group
- Study to be performed by 3 or more Laboratories.
- Albuterol HFA MDI product to be used for the study.

Objectives of 2nd Experiment

- **Demonstrate that the precision of the abbreviated impactor (AIM) is at least as good as the full-resolution impactor (ACI) in multiple laboratories.**
- **Assess variability of each impactor configuration, adjusted for batch, day and laboratory.**

2nd Study Overview

Four-day study, with 3-analyst team, balanced testing across two different impactor systems.

- **Full-resolution 8-stage Andersen cascade impactor (ACI)**
- **Abbreviated impactor (AIM) for Quality Control (QC) metric**

2nd Experiment Design

- Testing Scheme (for each day w/in a laboratory)

Sequence	Batch #	Inhaler #	Actuation Set	
			ACI	AIM
1	1	1	Set 1	Set 2
2	2	1	Set 2	Set 1
3	2	2	Set 1	Set 2
4	1	2	Set 2	Set 1

2nd Study Status & Next Steps

- Participating Laboratories to date are: BI, Melbourn Scientific (CRO-UK) &?
 - Additional laboratories: IPAC-RS members company and/or CRO non-member companies to participate in the 2nd study are to be identified
- Planning and scheduling of the protocol in each laboratory is in progress.

Acknowledgements

- Dave Christopher & Jorge Quiroz, Merck
- Jolyon Mitchell & Mark Nagel, TMI
- Helen Strickland, GSK
- Svetlana Lyapustina, IPAC-RS

- Members of the IPAC-RS Cascade Impaction Working Group

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- **Thank you**