



# Regulatory Perspectives on Abbreviated Impactor Testing (AIM)

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IPAC-RS Satellite Conference  
Berlin, May 6, 2011



# APSD Testing

- The FDA 1998 guidance recommends
  - Cascade impactors within NDAs be of the same design
  - Control temperature and relative humidity
  - Number of actuations based on sensitivity of method
  - Drug substance deposited on the critical stages of the cascade impactor should be characterized
  - Acceptance criteria proposed in terms of appropriate groupings of stages
  - MMAD, GSD, *respirable fraction*, *respirable dose*, or *fine particle mass* are not considered adequate to characterize the particle size distribution of the whole dose

## Typical APSD Specifications

	Stage Groups	Acceptance Criteria
1	Group 1 (Adaptor- S0)	20-40 mcg
2	Group 2 (S1-S3)	NMT 15 mcg
3	Group 3 (S4-S6)	25-50 mcg
4	Group 4 (S7-Filter)	NMT 10 mcg

## Cutoffs for Cascade Impactors at 60L/min

	Andersen*	MMI (Model M160)	MSLI	NGI
Preseparator	6.8			
Stage 0	6.2			
Stage 1	4.0	10.0	13	8.29
Stage 2	3.2	5.0	6.8	4.51
Stage 3	2.3	2.5	3.1	2.85
Stage 4	1.4	1.25	1.7	1.67
Stage 5	0.8	0.625		0.95
Stage 6	0.5			0.56
Stage 7	0.3			0.34
Filter				0.12

ECD ( $D_{50}$ ) estimations at other flow rates

$$D_{50,Q} = D_{50,QR} (Q_R / Q)^{1/2}$$

where

$D_{50,Q}$  is the cutoff diameter at the new flow rate, Q,

$D_{50,QR}$  refers to the cut off diameter at the reference flow rate  $Q_R$

## Current Trends in APSD Testing



Vs.



ACI

AIM

Pictures: Courtesy: ACI -- Ed Warner, Process Drift, PQRI FDA Workshop Dec. 2010  
C-FSA (Fast Screening Anderson) Copley Scientific, Inhalationmag.com, June 2009

IPAC-RS Satellite Conference  
RDD Europe 2011

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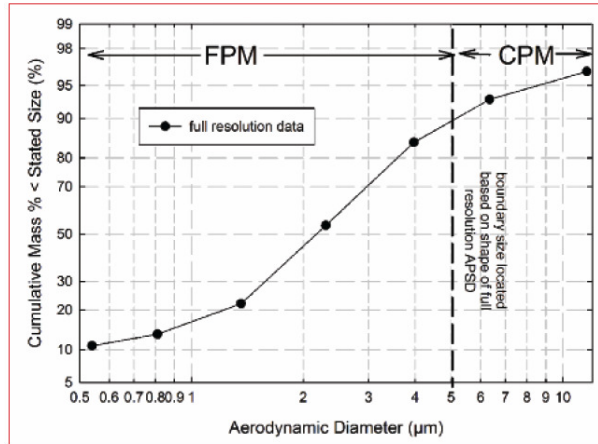
## AIM Concept

- In 2009/2010 concepts of AIM approach was proposed by IPAC-RS for routine Quality Control.
- Traditional multistage cascade impaction methods for measuring APSD is
  - labor intensive,
  - operator inconsistency can make them subject to measurement variability.
- May facilitate Quality-by-Design studies and creation of the Design Space.
- Briefing document included papers published by Tougas et al in *AAPS PharmSciTech*

The abbreviated impactor measurement concept, Jolyon P.Mitchell, Mark W.Nagel, and Mark Copley  
Inhalation 2009

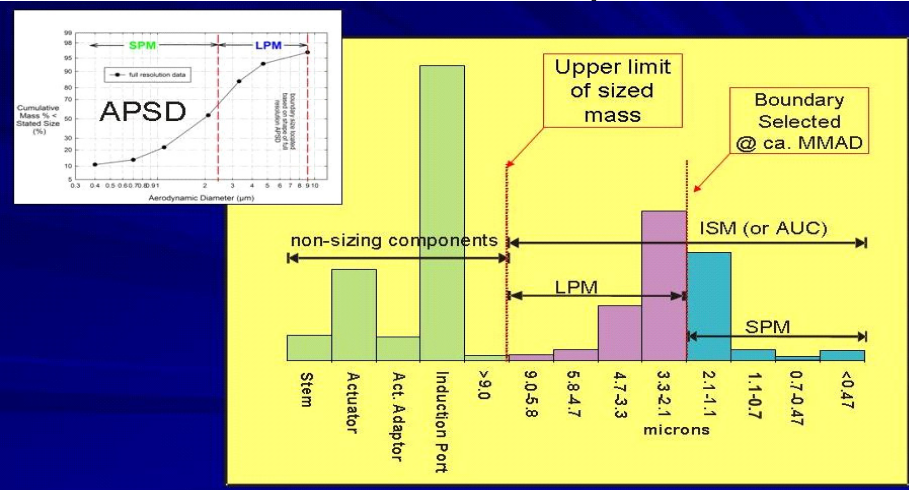
# AIM Concept

- AIM concept reduces the 7 or 8 data points associated with the typical full resolution APSD to the 2 mass fractions assigned to fine (FPM) and coarse (CPF) particles.



The abbreviated impactor measurement concept, Jolyon P. Mitchell, Mark W. Nagel, and Mark Copley Inhalation 2009

# AIM Concept



Tougas et al, USP, Aerodynamic Particle Size Testing of Orally Inhaled Products: Abbreviated Impactor Measurements and Efficient Data Analysis (AIM/EDA) Dec 2010

## IPAC-RS meeting July 2010

- Contained data on 8 products (HFA MDI solution, 2 HFA MDI suspension, 2 DPIs, 3 CFC Suspensions).
- Publication claims that
  - The time required is greatly reduced
  - Improved overall precision
  - Improve quality decisions, i.e., batch disposition.
  - Time savings associated with AIM systems may increase samples evaluated from a batch within a fixed timeframe
  - Reducing the number of manipulations decrease the chances of operator-related errors.
  - Environmentally friendly by using less solvents
  - Simpler apparatus configurations that are more amenable to automation

## Statistical Concerns on AIM

- Statistical concerns about APSD portions (large and small particle masses) may be positively correlated to ISM.
- Multiple distributions can share the same LPM/SPM ratio.
- Uni-modal and bimodal distributions may share the same mean and variation.
- While it reduces variability in measurements it comes with loss of full information
  - QC test based on only two measures considers less information than current test



## Conclusions

- AIM is useful as a research tool for quick analysis!
- FDA recognizes that AIM will save time and hence better throughput.
- If the issues highlighted by the statisticians are addressed there is scope to consider AIM and EDA as a important analytical tool.
- The Agency believes that better science should lead to better regulations and are open to discussion to alternative approaches to control strategies.