



Welcome
IPAC-RS Workshop
AIM/EDA – Implementing a New Best Practice
for OIP Aerosol Particle Size Analysis

Terrence P. Tougas

on behalf of the
IPAC-RS Cascade Impactor Working Group

Goals of Workshop

- Provide info on work of Cascade Impactor Working Group related to AIM/EDA
- Seek feedback from participants on this initiative
- Encourage exploration and possible adoption of AIM/EDA concepts



LIFECYCLE STRATEGIES FOR USING EDA, AIM AND FULL RESOLUTION IMPACTOR

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Overview

- AIM-EDA was designed to be one element of an overall APSD strategy for the development and commercialization of an Orally Inhaled Product (OIP)
 - Designed primarily to be used as a Quality Control test
- Goal of this talk is to explore proposed role of AIM-EDA and other tests in relation to the Product Development/Commercialization Lifecycle
- AIM-EDA designed to answer question:
Is the APSD 'normal' or 'abnormal'?

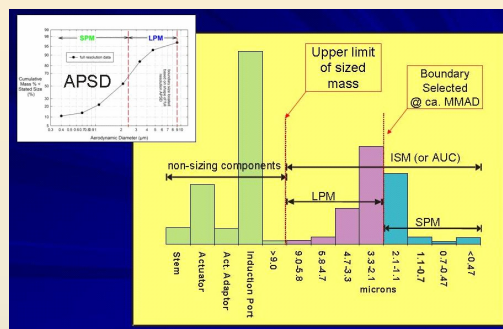
APSD: Characterization, QC and Bioequivalence

APSD measured for...	Product characterization	Product quality control	In-vitro Bioequivalence
Which physical product is tested?	A product under development	Approved and understood product	Two different products (e.g., from different manufacturers or of different designs)
What is the question you are trying to answer?	What is the distribution? What factors affect it? How does it change? What is the typical range?	Is the distribution essentially the same as before?	Are there any clinically important differences between two distributions?
When are you measuring it?	During product development	At the end of every manufacturing run	When studying and developing a new product
Impactor to use	Full resolution	Full resolution or AIM	Full resolution
Statistical approaches	A number of approaches	EDA or group stages (US) or FPD (EU)	PBE?

Defining Efficient Data Analysis (EDA)

Relies on Two Metrics:

- Impactor sized Mass (ISM)
- Ratio of large to small particle mass (LPM/SPM)
- Independent, non-confounded metrics
 - Related to **Mean** and **Area** of APSD
 - In contrast with stage groupings or fine particle dose



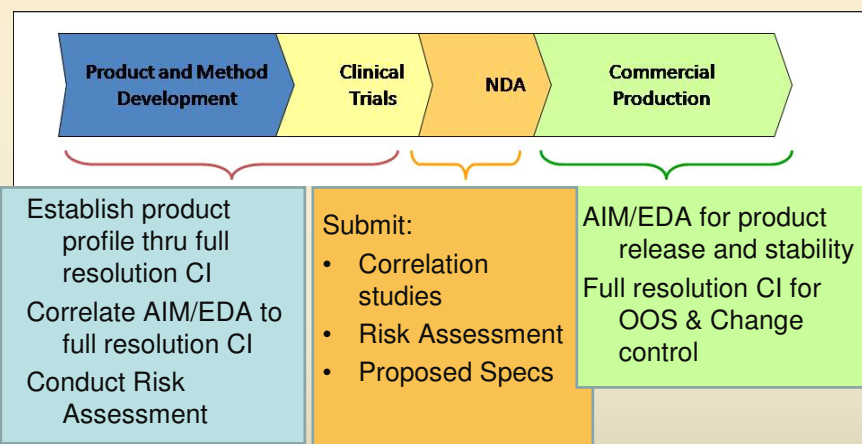
EDA metrics can be obtained with either Full Resolution Impactor or AIM device

Questions

- Will AIM/EDA eliminate the need for multi-stage impactors?
- Does AIM/EDA add additional requirements to release/stability testing?
- How does one set acceptance criteria for EDA?
- Will regulatory authorities accept AIM/EDA?
- What are the advantages of AIM/EDA over current expectations (Grouped stages - US; Fine particle dose - Europe)?
- Is AIM/EDA proposed as a mandatory requirement – US? ROW?

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Proposed Lifecycle



T. P. Tougas, D. Christopher, J. Mitchell, S. Lyapustina*, M.I Van Oort, R. Bauer, and V. Glaab,
Product Lifecycle Approach to Cascade Impaction Measurements, AAPS PharmSciTech., DOI:
10.1208/s12249-011-9590-5

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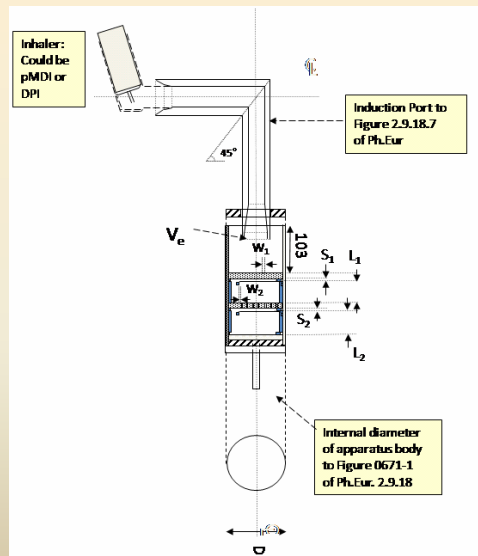
AIM-pHRT

- AIM-pHRT - Abbreviated Impactor Measurement – potential Human Respiratory Tract
- Much discussion about potential to establish *in vivo* relationship to an AIM based measurement
- EU fine particle dose crude attempt along these lines
- Availability would aid investigations, change control, product development, qualifying add on devices...

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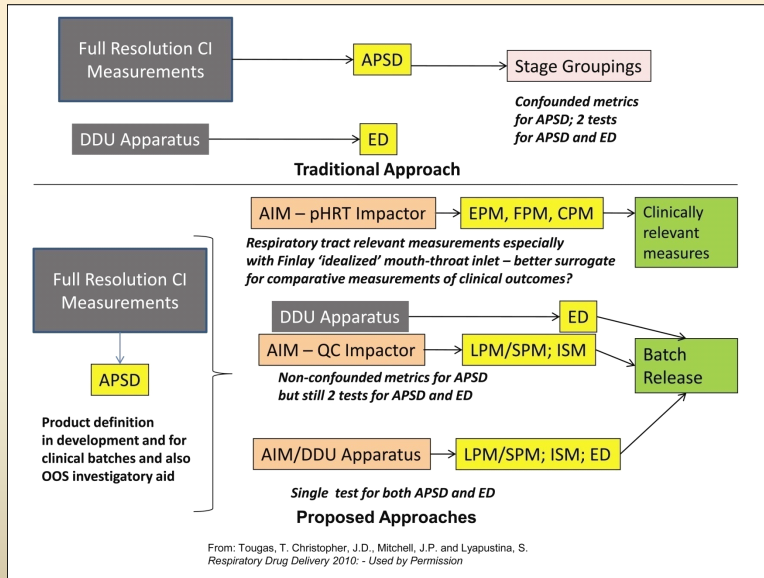
Combination of AIM and DDU

- The measurement of delivered dose uniformity (DDU) could ultimately also be included in the relationship between these systems and existing techniques
- There is the potential to combine both DDU and abbreviated APSD measurements into a single apparatus



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Integration of AIM-EDA and DDU



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Lifecycle - Development

- APSD characterized with full-resolution CI based measurements
 - Multiple batches and samples sufficient to establish target product APSD and associated variability
- Establish proposed EDA Metrics for QC through selection of 'cut-point'
 - LPM/SPM & ISM (=LPM+SMP)
 - Cut-point generally selected to give maximum sensitivity to changes in MMAD (i.e. LPM/SPM~1)
- Consider establishing in vivo-relevant metrics (AIM-pHRT – CPM, FPM, EPM)

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Lifecycle – Experimental Use of AIM in Development

- Prior to approved use of AIM-EDA as part of OIP control strategy may be useful for:
 - Formulation optimization or screening
 - Process development
 - Device design
- AIM-pHRT may serve a similar role prior to establishing *in vivo* relationship

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Lifecycle – Establishing AIM-EDA

- ‘Validate’ EDA Metrics and AIM
 - Demonstrate linearity between LPM/SPM and MMAD
 - Characterize precision of LPM/SPM and ISM determinations
 - Demonstrate accuracy of AIM relative to multistage impactor (applies to both QC and pHRT variants)
- Conduct a risk assessment to understand potential factors that might impact APSD
 - Assess ability of AIM-EDA to detect
 - Mitigate risk

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Lifecycle - Introducing AIM-EDA into Control Strategy

- Establish appropriate limits for LPM/SPM and ISM
- Individual Company decision as to when to seek approval of AIM-EDA as part of 'control strategy'
 - Release of clinical supplies
 - Stability Studies
 - Introduced as part of part of NDA/MAA
 - Post approval change to control strategy

Life Cycle – Investigations and Change Control

- Once AIM-EDA approved it would be the primary QC test for APSD
- However continuing role for full resolution multistage CI method
 - Investigations (OOS/OOT results)
 - Support changes (process, materials)
 - Periodically to verify the LPM/SPM ratio?
- AIM-pHRT may serve a similar role if *in vivo* relevance has been established

Acknowledgements

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- Michiel Van Oort, Richard Bauer, Volker Glaab - Co-authors on PharmSciTech Lifecycle paper
- Members of the IPAC-RS Cascade Impaction Working Group

The End

