



# **Lifecycle Aspects of Incorporating AIM-EDA into Development Cycle**

## **Q&A Technical Aspects**

IPAC-RS Cascade Impaction Working Group

## **Agenda**

1. Background information
2. Applicability of the AIM-EDA concept in OIP Life-cycle management
3. Panel Discussion: Technical Aspects of AIM-EDA

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J. David Christopher, Merck, Kenilworth, NJ, USA  
Volker Glaab, Ph.D, Boehringer Ingelheim,  
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Jolyon Mitchell, Ph.D., Trudell Medical International,  
London, Ontario, Canada

## CI WG Members

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3. Volker Glaab **BI**
4. Rajni Patel **Boehringer Ingelheim**
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9. Francesca Usberti **Chiesi**
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13. Helen Strickland **GlaxoSmithKline**
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15. Dave Christopher **Merck**
16. Monisha Dey **Merck**
17. Adrian Goodey **Merck**
18. Jorge Quiroz **Merck**
19. Nagaraja Rao **Novartis**
20. Dave Russell-Graham **Pfizer**
21. Hans Keegstra **Teva**
22. Zecai Wu **Teva**
23. Jolyon Mitchell **Trudell Medical International**
24. Bruce Wyka, **SpiraPharma Consulting**
25. Adam Watkins, **Vectura**

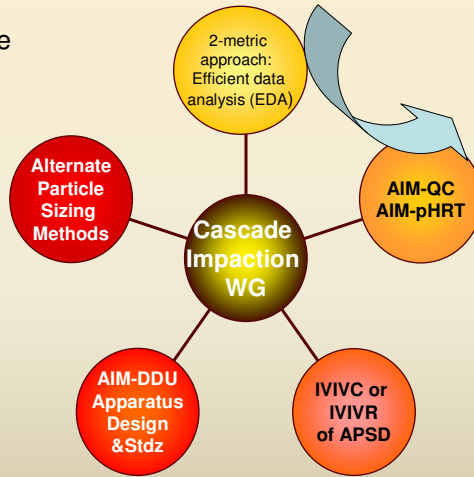
## Overall Objectives of IPAC-RS CI WG

1. To develop and disseminate recommendations for more effective methods for APSD testing and analysis of data
2. To support more effective decision making regarding APSD of OINDP in the contexts of product development and QC

# Areas of Interest

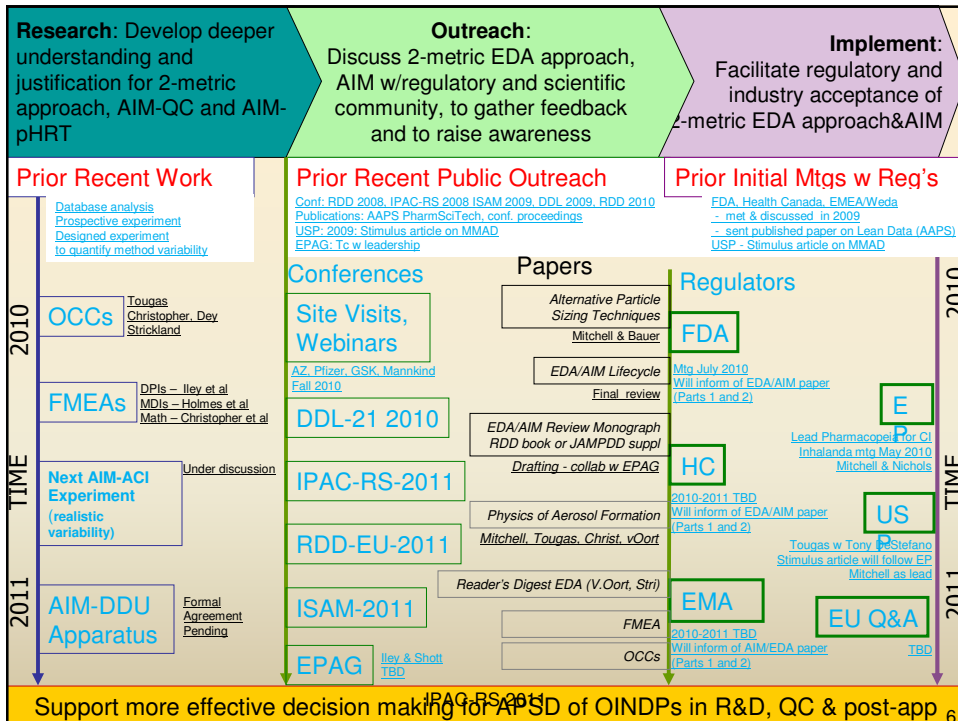
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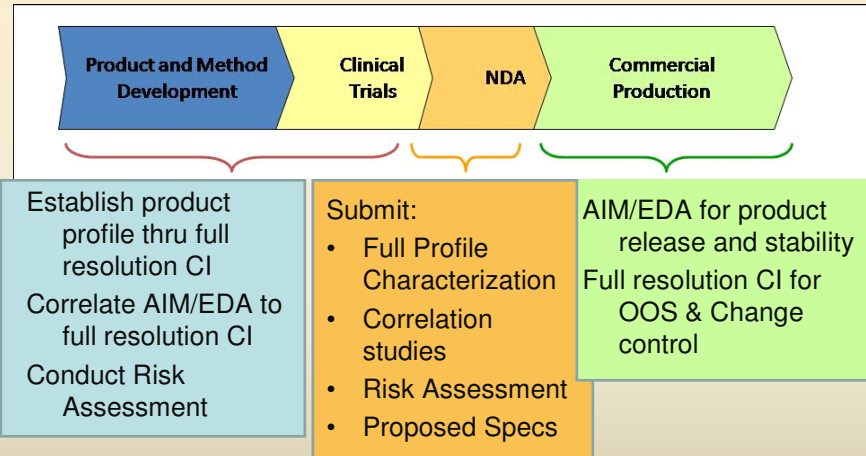
## CI WG Presentations & Symposia

- **USP Particle Size Detection and Measurement**, 8-10 December 2010, Rockville, MD (<http://www.usp.org/pdf/EN/meetings/workshops/2010ParticleAgenda.pdf>):
  - 4 Presentations: EDA/AIM, foreign particles.
- **DDL-21**, 8-10 December 2010, Edinburgh, Scotland, UK (<http://ddl-conference.org.uk/>):
  - Presentation about experimental aspects.
- **IPAC-RS 2011**, March 29-31, Rockville MD (<http://www.ipacrs.com/2011%20Conference.html>):
  - A presentation on alternative particle sizing techniques in the main program.
  - For the full-day CI workshop:
    - AIM/EDA lifecycle story, attention to FDA's group stages, discussions with FDA scientists.
    - In addition to FDA, invite M. Weda (EMA) and K. Tirunellai (Health Canada) for a regulatory panel.
- **RDD-EU-2011**, May 3-6, Berlin, Germany (<http://www.rddonline.com/rdd/rdd.php?id=6>):
  - Presentation(s) on OCCs and FMEAs in the main RDD program; and
  - Discussion of EDA vs FPM in the post-RDD interactive session (CI Symposium).
  - NOTE: Other workshops on AIM?
- **ISAM 2011**, June 18-22, Rotterdam, Netherlands (<http://www.isam2011.com/>):
  - IVIV relationships for AIM-pHRT.

## 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?

## 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

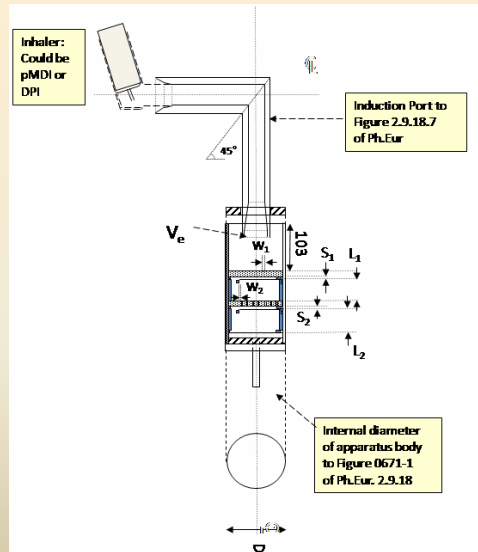
- AIM-pHRT - Abbreviated Impactor Measurement – potential Human Respiratory Tract
- Much discussion about potential to establish *in vivo* relationship to an AIM based measurement
- EU fine particle dose crude attempt along these lines
- Availability would aid investigations, change control, product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

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## Combination of AIM and DDU

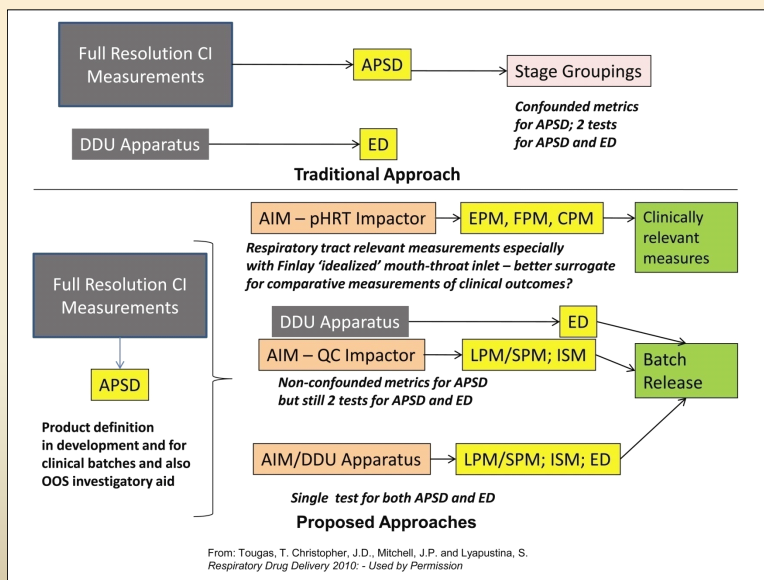
- The measurement of delivered dose uniformity (DDU) could ultimately also be included in the relationship between these systems and existing techniques
- There is the potential to combine both DDU and abbreviated APSD measurements into a single apparatus



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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
  - 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)

## Lifecycle – Establishing AIM-EDA

- ‘Validate’ EDA Metrics and AIM
  - Demonstrate relationship 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

## Lifecycle – Experimental Use of AIM in Development

- Prior to approved use of AIM-EDA as part of OIP control strategy AIM and/or EDA 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

## Lifecycle – Content of Regulatory Submission

- Full Profile Characterization
  - Sufficient multistage impactor data to establish both the target APSD and expected normal variability of APSD
- Validation studies
  - Accuracy, precision of AIM method
  - Establish relationship of EDA metrics to multi-stage impactor data and particle size distribution parameters
- Risk Assessment of Product and Ability of EDA to Detect Aberrant Product
- Justification of EDA acceptance criteria
  - Derived from current expectations
  - *In vivo/in vitro* relationship???

## 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

- IPAC-RS member companies
- Dave Christopher, Jolyon Mitchell, Svetlana Lyapustina,
- Michiel Van Oort, Richard Bauer, Volker Glaab - Co-authors on PharmSciTech Lifecycle paper
- Members of the IPAC-RS Cascade Impaction Working Group

## The End



## Introduce Panel

William Doub, Ph.D., US FDA, St. Louis, MO, USA

J. David Christopher, Merck, Kenilworth, NJ, USA

Volker Glaab, Ph.D, Boehringer Ingelheim, Ingelheim am Rhein, Germany

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## 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?