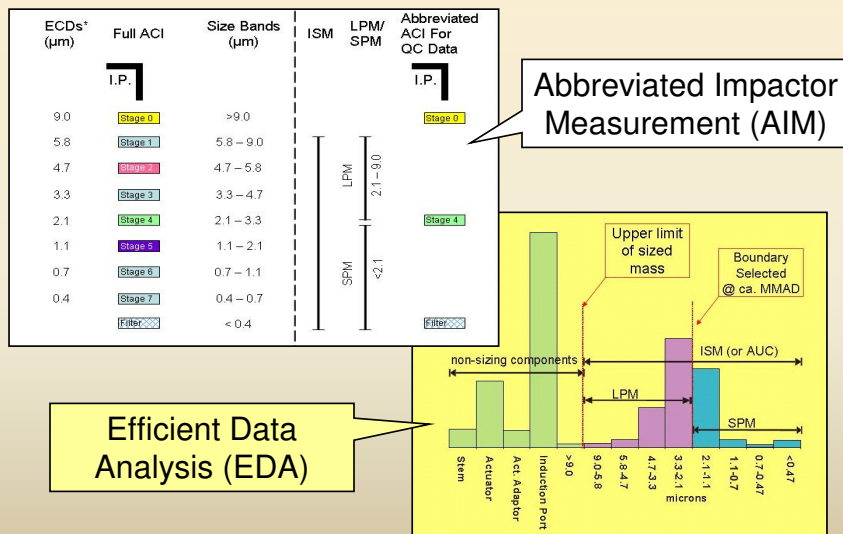




Road to Adopting AIM-EDA as a Standard

Adrian Goodey
 on behalf of the
 IPAC-RS Cascade Impactor Working Group
 31 March 2011

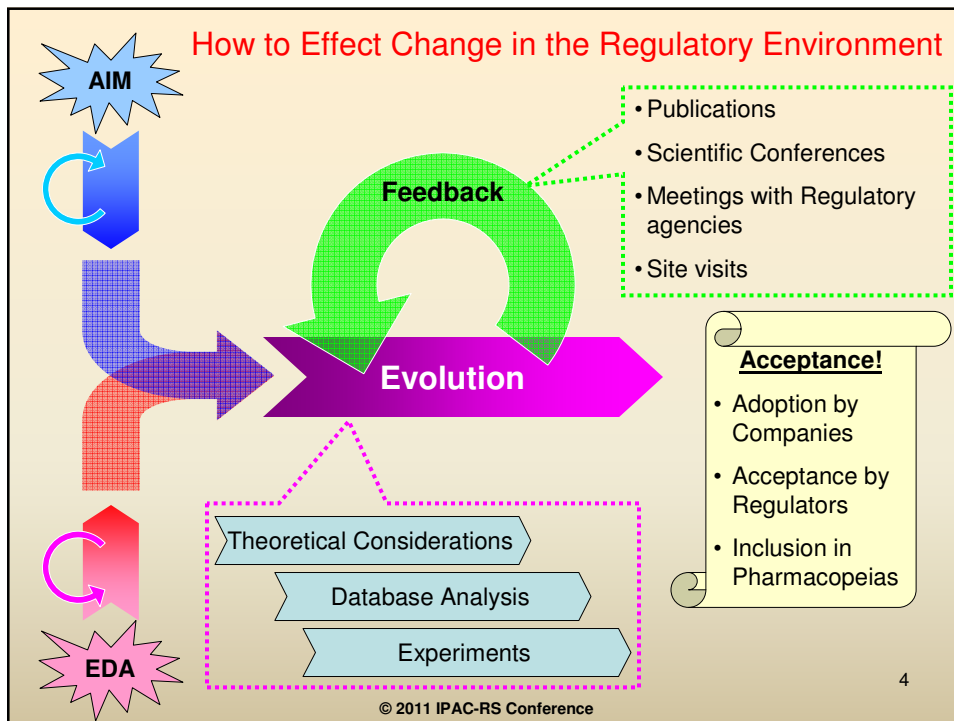
AIM-EDA Background



How to Effect Change in the Regulatory Environment?



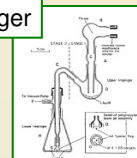
- Challenge: convince stakeholders...
 - No increased risk or decreased benefit for patients
 - Improved QC decision making
 - Time and resource savings



AIM Background

- Motivation for Abbreviated Impactors
 - More rapid aerodynamic assessment of OIPs
 - More robust process

Twin Impinger



Copley Short-Stack Fast Screening Andersen Impactor



Courtesy Copley Scientific

Westtech Short-Stack Fine Particle Dose Impactor



Courtesy Westtech Instrument Services



Courtesy MSP Corp.

MSP Fast Screening Impactor

© 2011 IPAC-RS Conference

AIM Evolution: Precision Experiments

Study Purpose:

- The precision study was undertaken to characterize the relative variability of two different abbreviated impactors versus a full-resolution ACI:
 1. AIM-QC system for OIP quality control testing
 2. AIM-pHRT system for possible use in characterizing clinically relevant metrics related to particle deposition in different regions of the human respiratory tract

AIM Evolution: Precision Experiments

- Work recently published in *AAPS PharmSciTechnol.*

Mitchell *et al.*
contains key details
AAPS PharmSciTechnol.,
2010;11(2):843-851.

AAPS PharmSciTech, Vol. 11, No. 2, June 2010 (© 2010)
DOI: 10.1208/s12249-010-9432-6

Research Article

Relative Precision of Inhaler Aerodynamic Particle Size Distribution (APSD) Metrics by Full Resolution and Abbreviated Andersen Cascade Impactors (ACIs): Part 1

Jolyn P. Mitchell,¹ Mark W. Nagel,¹ Cathy C. Doyle,¹ Robina S. Ali,¹ Valentina I. Avvakoumova,¹ J. David Christopher,² Jorge Quiroz,² Helen Strickland,² Terrence Tougas,³ and Svetlana Lyapunina^{2,6}

Received 30 December 2009; accepted 27 April 2010; published online 18 May 2010

Abstract. The purpose of this study was to compare relative precision of two different abbreviated impactor measurement (AIM) systems and a traditional multi-stage cascade impactor (CI). The experimental design was chosen to provide separate estimates of variability for each impactor type. Full-resolution CIs are useful for characterizing the aerosol aerodynamic particle size distribution of orally inhaled products during development but are too cumbersome, time-consuming, and resource-intensive for other applications, such as routine quality control (QC). This article presents a proof-of-concept experiment, where two AIM systems configured to provide metrics pertinent to QC (QC-system) and human respiratory tract (HRT-system) were evaluated using a hydrofluoroethane-albuterol pressurized metered dose inhaler. The Andersen eight-stage CI (ACI) served as the benchmark apparatus. The statistical design allowed estimation of precision with each CI configuration. Apart from one source of systematic error affecting extra-fine particle fraction from the HRT-system, no other bias was detected with either abbreviated system. The observed bias was shown to be caused by particle bounce following the displacement of surfactant by the shear force of the airflow diverging above the collection plate of the second impaction stage. A procedure was subsequently developed that eliminated this source of error, as described in the second article of this series (submitted to *AAPS PharmSciTech*). Measurements obtained with both abbreviated impactors were very similar in precision to the ACI for all measures of *in vivo* performance evaluated. Such abbreviated impactors can therefore be substituted for the ACI in certain situations, such as inhaler QC or *in vitro* device testing.

KEY WORDS: AIM, APSD, impactor, inhaler, simplified.

AIM Evolution: Precision Experiments

Conclusions/Findings:

- Work demonstrated comparable precision of AIM-QC, AIM-HRT and multi-stage ACI
- With exception of extra fine fraction in AIM-HRT, no bias among different impactor configurations was observed
 - Issue of bias in extra-fine particle size fraction was subsequently studied, resolved and was subject of a second publication

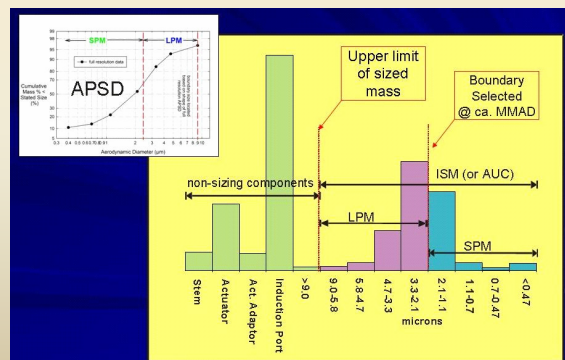
EDA Origin

- Goal: Investigate alternative methods that are better able to detect changes in APSD for Quality Control (QC) purposes
 - An elaboration of the proposed “grouped stages” approach, with some refinements

© 2011 IPAC-RS Conference

EDA Origin

- Impactor sized Mass (ISM)
- Ratio of large to small particle mass (LPM/SPM)
- Independent, non-confounded metrics
 - In contrast with stage groupings
 - Readily accessible with AIM-based technology



© 2011 IPAC-RS Conference

EDA Evolution: Retrospective Verification

- The approach was refined through a comparison of metrics performance by assessing CI results from an IPAC-RS database
 - Database includes >3600 APSD results submitted by industry spanning many products and different dosage forms

© 2011 IPAC-RS Conference

EDA Evolution: Retrospective Verification



Goals

- See if simpler metrics are capable of detecting changes in both MMAD and impactor sized mass (ISM)
 - Refine complex APSD data to essential metrics
 - Avoid confounding
- Focus is on QC setting

Method

- Retrospective analysis of OIP database

Tougas *et al.*
AAPS PharmSciTechnol.,
 2009;10(4):1276-1285

© 2011 IPAC-RS Conference

12

EDA Evolution: Retrospective Verification

Conclusions

- The proposed set of metrics (LPM/SPM and LPM+SPM) is:
 - Direct
 - Practical
 - Easy to implement
 - Sensitive to APSD changes
 - Compared to stage groupings, is a better decision making tool
 - Well aligned with AIM concepts

AIM-EDA Evolution

- **Goal**
 - Investigate alternative methods that are **better able to detect changes in APSD** for Quality Control (QC) purposes
- **Ongoing Efforts**
 - Theoretical Considerations
 - Database Analysis
 - Laboratory Experiments

AIM-EDA Evolution

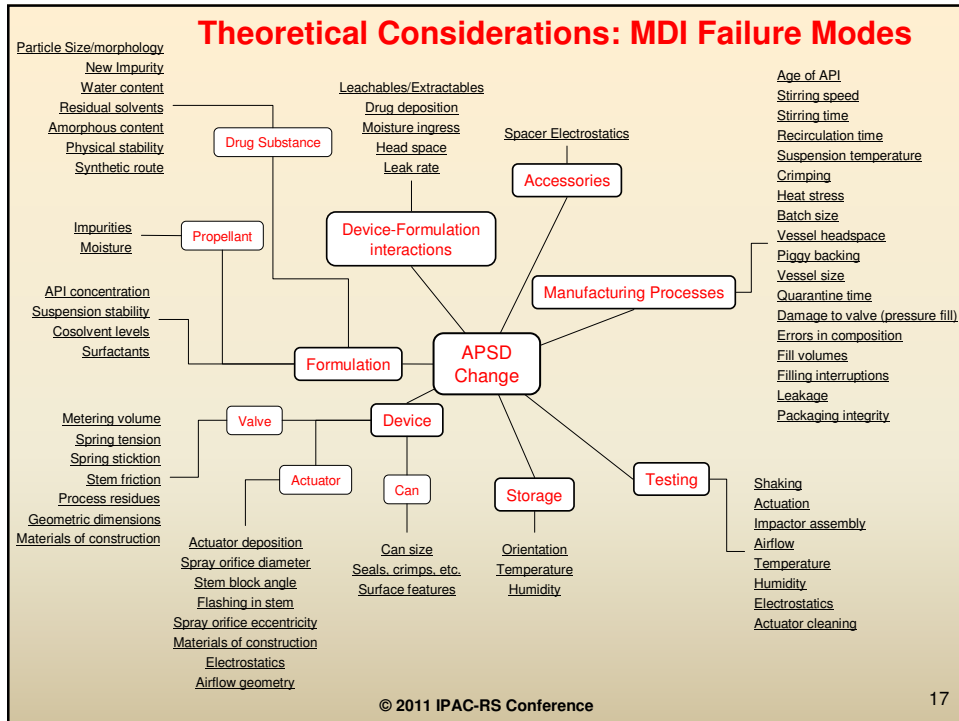
- Theoretical Considerations
 - What changes in shape of APSD and under what circumstances would EDA not detect
 - Physical phenomena that impact aerosols
 - e.g. agglomeration, gravitational sedimentation, inertial impaction, Brownian diffusion, turbulent diffusion, phoretic processes, electrostatic charge
 - Failure mode effect analysis of OIPs

15

Theoretical Considerations: Changes in APSD

Nature of Change	ACI Observation	Conditions Required for EDA Failure
Increasing MMAD	Shift in mass from lower plates to higher plates	entire APSD contained within either LPM or SPM
Decreasing MMAD	Shift in mass from higher plates to lower plates	entire APSD contained within either LPM or SPM
Broadening APSD (constant MMAD, AUC)	decreased mass on central plates, increased mass on peripheral plates	LPM/SPM boundary = MMAD OR entire APSD contained within either LPM or SPM
Narrowing APSD (constant MMAD, AUC)	increased mass on central plates, decreased mass on peripheral plates	LPM/SPM boundary = MMAD OR entire APSD contained within either LPM or SPM
Change in Shape	Change in mass distribution across plates, change in MMAD	entire APSD contained within either LPM or SPM
Change in Modality (unimodal → bimodal)	emergence of mass at new mode, balanced by decreased mass at original mode	entire APSD contained within either LPM or SPM
Increasing AUC	Increased mass across all plates	---
Decreasing AUC	Decreased mass across all plates	---

16



AIM-EDA Theoretical Considerations

Tentative Conclusions:

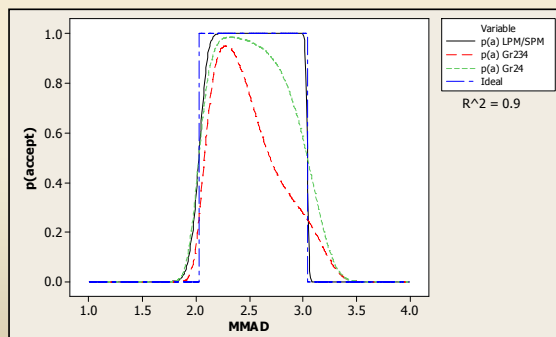
- No plausible scenario exists for a change in APSD that would not be detected by the proposed EDA metrics
- The sponsor of a product would undertake due diligence to check for 'failure-to-detect' scenarios as part of method development involving AIM-EDA

AIM-EDA Database Analysis

- Operating Characteristics Curves:
assessing the performance of EDA vs.
stage groupings
 - Two strategies currently being explored
 - Designed to evaluate tests, not products

AIM-EDA Evolution

- Operating Characteristics Curves



OCCs comparing ability of LPM/SPM to detect changes in MMAD versus grouped stages

LPM/SPM well-suited to support assumed limits
Grouped stages unable to support assumed limits

Eliminating middle stage is improving overall stage grouping approach

AIM-EDA Evolution

- Planned Laboratory Experimentation
 - characterize relative variability of the full resolution Andersen cascade impactors (ACI) and the Abbreviated Impactor Measurement for Quality Control (AIM-QC) system using a pressurized metered dose inhaler (pMDI)
 - determine how well the efficient data analysis (EDA) functions as a decision-making tool when determining batch quality
 - span widest possible range of characteristics of a commercial product

21

© 2011 IPAC-RS Conference

AIM-EDA Evolution

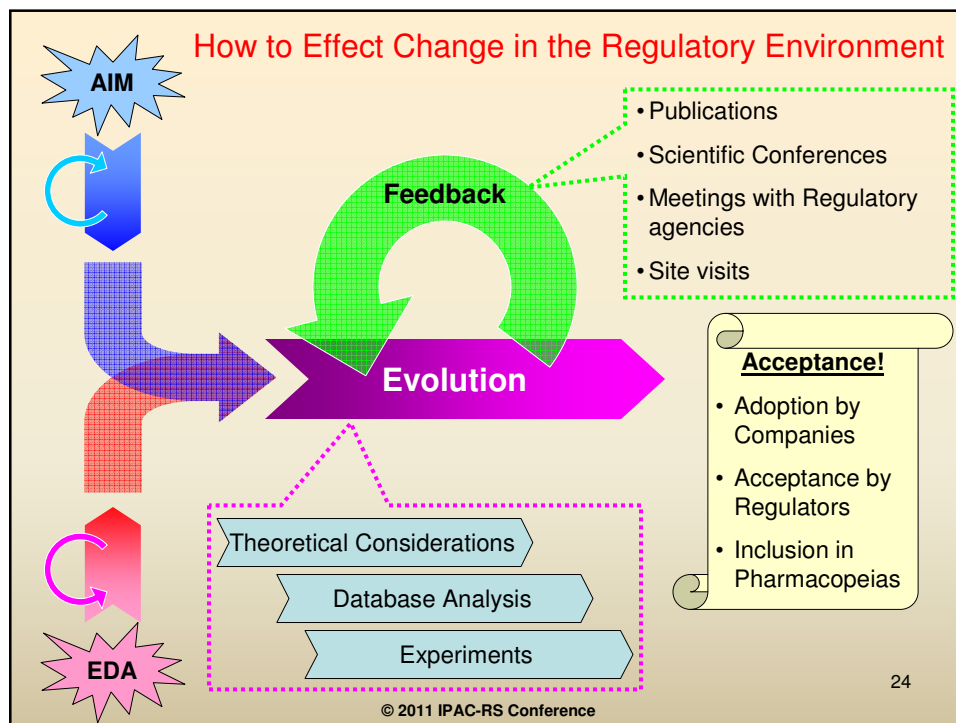
- Outreach & Feedback
 - Publications
 - Scientific Conferences
 - Meetings with Regulatory Authorities & Pharmacopeias
 - Site Visits

22

© 2011 IPAC-RS Conference

AIM-EDA Evolution

- Meetings with Regulatory Authorities & Pharmacopeias
 - Initial activities concerning both AIM and EDA Concepts were discussed with key agencies
 - FDA/CDER (21 September 2009)
 - Health Canada (13 Nov 2009)
 - EMEA (17 Nov 2009)
 - Regulatory and pharmacopeial discussions
 - FDA/CDER (28 July 2010)
 - EMA (telecon on 10 September 2010)
 - USP (Expert Committee Mtg, August 2010)



CI WG Members

1. Steve Stein **3M**
2. Mårten Svensson **AstraZeneca**
3. Volker Glaab **BI**
4. Rajni Patel **Boehringer Ingelheim**
5. Terry Tougas **BI (CHAIR)**
6. Tanya Church **Chiesi**
7. David Lewis **Chiesi**
8. Emilio Lutero **Chiesi**
9. Francesca Usberti **Chiesi**
10. Lana Lyapustina **DBR**
11. Geoff Daniels **GlaxoSmithKline**
12. Sue Holmes **GlaxoSmithKline**
13. Helen Strickland **GlaxoSmithKline**
14. Richard Bauer **MannKind Corporation**
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**