



OVERVIEW OF EFFECTIVE DATA ANALYSIS (EDA)

Terrence P. Tougas

on behalf of the
IPAC-RS Cascade Impactor Working Group

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25. Bruce Wyka, **SpiraPharma Consulting**

Overall Objective of AIM-EDA

To support more effective decision making
regarding APSD of OINDP in the
contexts of product development and QC

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?

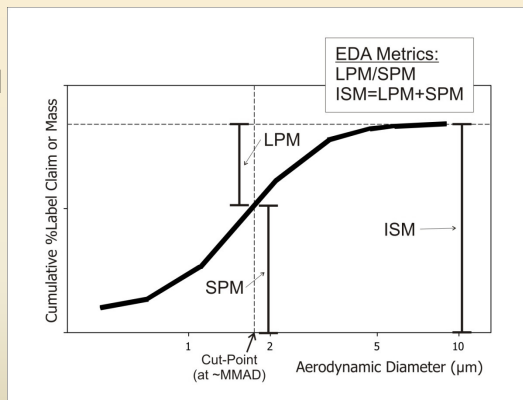
EDA - Review



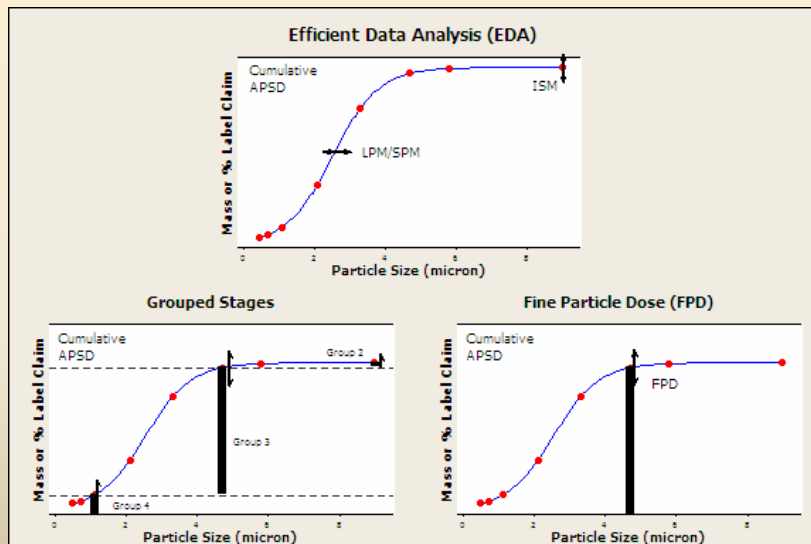
- Application is primarily on product quality control:
 - similar approach could equally be applied to metrics with more direct clinical relevance, such as coarse, fine and extra-fine particle fractions
- Tougas *et al.* provides key details
 - *AAPS PharmSciTechnol.*, 2009;10(4):1276-1285.

EDA Metrics in Product QC

- 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



QC Metrics for APSD



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Selection of Boundary between LPM and SPM

- To date defining fine and coarse particle mass/fraction considered loosely from a physiological perspective *
- By contrast, the purpose here is to detect quality changes in APSD. Therefore the LPM-SPM boundary selected to maximize sensitivity to changes.

*Regional particle deposition processes in the respiratory tract, though size-selective are not sharply so (Heyder, J., J. Gebhart, G. Rudolf, *et al.* Deposition of particles in the human respiratory tract in the size range 0.005–15 μm . *J. Aerosol Sci.* 1986;17:811–825.)

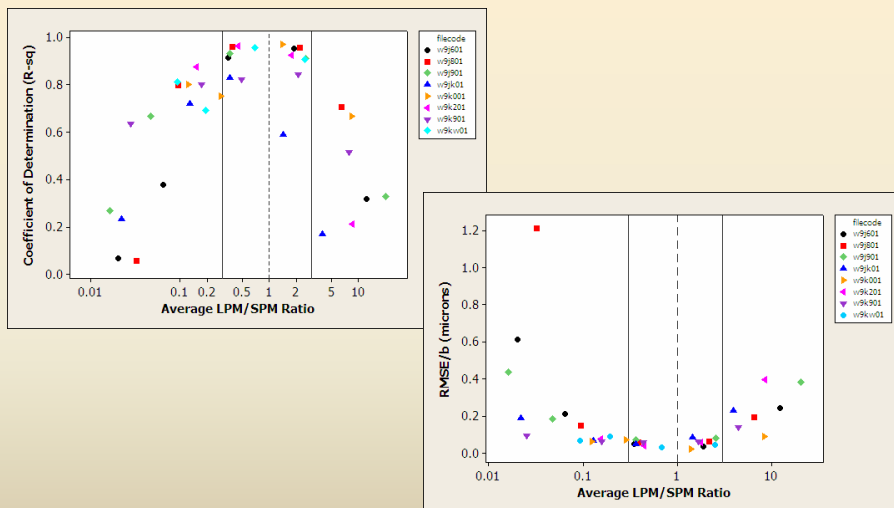
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Selection of Boundary between LPM and SPM (cont'd)

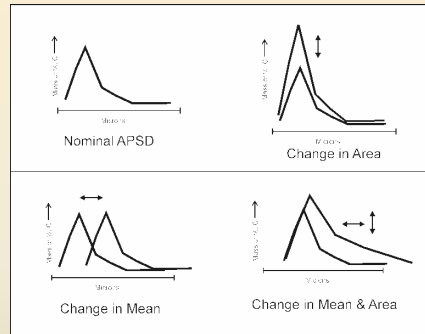
- Theoretically, the greatest sensitivity when the distribution is equally divided between large and small particle mass
 - i.e., at MMAD; LPM/SPM of unity
- To verify, regressions were obtained for eight products with boundaries selected between all stages for each product
- Results confirm highest sensitivity when LPM/SPM is about 1.0; however
- Relatively broad range where strong correlation exists i.e. approximately 0.3 - 3.0

Selection of Size Boundary



ISM and LPM/SPM in Relation to APSD

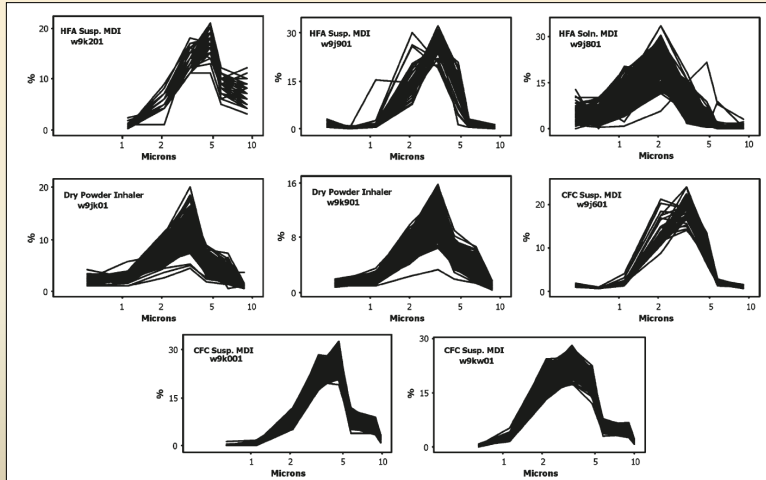
- ISM provides measure of area under the curve for the differential mass-weighted APSD
- Combination of ISM and LPM/SPM enables all forms of APSD shift to be detected



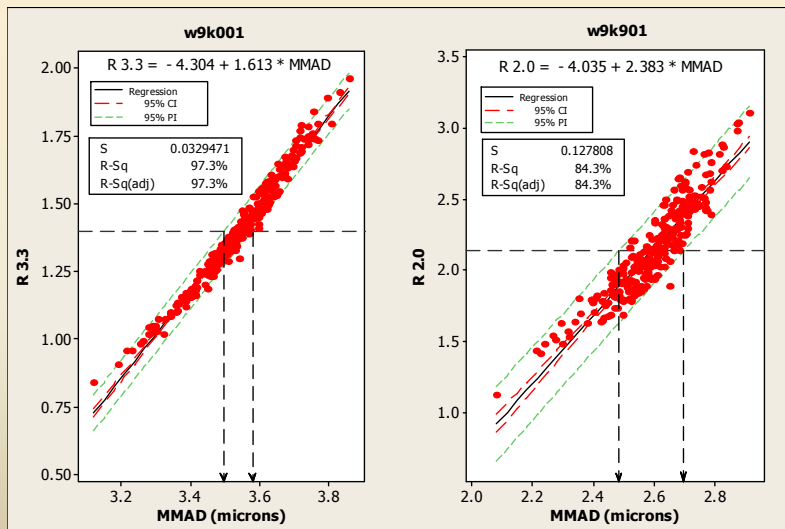
Benefits of EDA

- **An improved approach for control of OIP APSD changes with two separate and independent metrics:**
 - A metric sensitive to changes in the **mean**
 - A metric sensitive to changes in the **area under the APSD curve**

APSDs of Products Studied



Example Linear Regressions LPM/SPM vs. MMAD



Linear Regression Analysis: LPM/SPM vs. MMAD

Filecode	Product Type	CI runs (n)	Optimum Boundary (microns)	Avg. MMAD (microns)	Slope (b)	RMSE*	Coefficient of Determination R ² (%)	RMSE/b (microns)
w9k201	HFA Suspension MDI	80	4.7	3.91	0.407	0.0162	96.4%	0.040
w9j901	HFA Suspension MDI	39	3.3	2.57	0.4959	0.0350	93.4%	0.071
w9j801	HFA Solution MDI	201	2.1	1.5	0.7155	0.0421	96.2%	0.059
w9jk01	Dry Powder Inhaler	279	3.3	2.66	0.4319	0.0201	83.0%	0.047
w9k901	Dry Powder Inhaler	279	2.0	2.59	2.3831	0.1278	84.3%	0.054
w9j601	CFC Suspension MDI	43	2.1	2.54	2.4548	0.0872	95.5%	0.036
w9k001	CFC Suspension MDI	272	3.3	3.54	1.6127	0.0330	97.3%	0.020
w9kw01	CFC Suspension MDI	272	3.3	2.86	0.7046	0.0198	95.8%	0.028

*Root Mean Square Error

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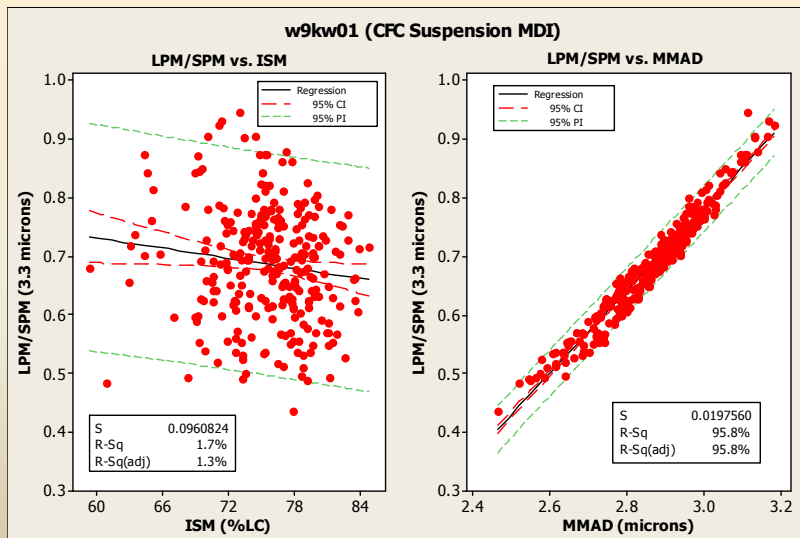
Summary of LRA Results LPM/SPM vs. MMAD

- Strong correlation between LPM/SPM and MMAD
 - R² ranged from 83.0% to 97.3%
 - All slopes positive
- RMSE/b values suggest that MMAD shifts of the order of 0.1-0.2 microns could be reliably detected

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Example Demonstrating Correlation of LPM/SPM with MMAD and Independence from ISM



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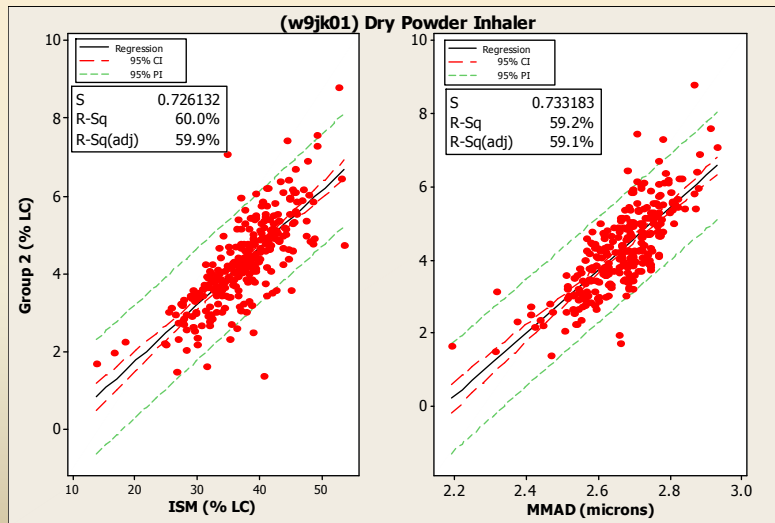
Correlation of LPM/SPM with MMAD and Independence from ISM

Filecode	Product Type	Regression Analysis: LPM/SPM Ratio vs. ISM				Goodness of Fit LPM/SPM Ratio vs. MMAD (at optimum boundary)	
		Slope (b)	RMSE*	Coefficient of Determination R ² (%)	RMSE/b (microns)	Coefficient of Determination R ² (%)	RMSE/b (microns)
w9k201	HFA Suspension MDI	0.005	0.082	7.4	16.4	96.4	0.040
w9j901	HFA Suspension MDI	0.003	0.136	1.0	45.3	93.4	0.071
w9j801	HFA Solution MDI	-0.012	0.185	27.2	-15.4	96.2	0.059
w9jk01	Dry Powder Inhaler	0.003	0.045	15.0	15.0	83.0	0.047
w9k901	Dry Powder Inhaler	0.039	0.263	33.9	6.8	84.3	0.054
w9j601	CFC Suspension MDI	0.017	0.406	2.9	23.9	95.5	0.036
w9k001	CFC Suspension MDI	0.003	0.202	0.4	67.3	97.3	0.020
w9kw0 1	CFC Suspension MDI	-0.003	0.096	1.7	-32.0	95.8	0.028

*Root Mean Square Error

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Confounded Response: Stage Groupings



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Preliminary Work on Operating Characteristics Curves (OCCs)

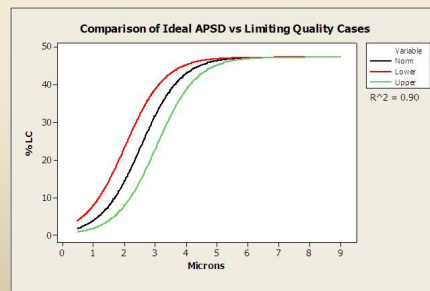
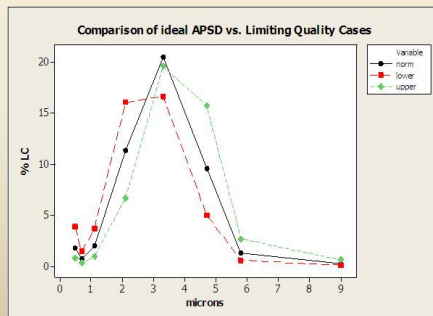
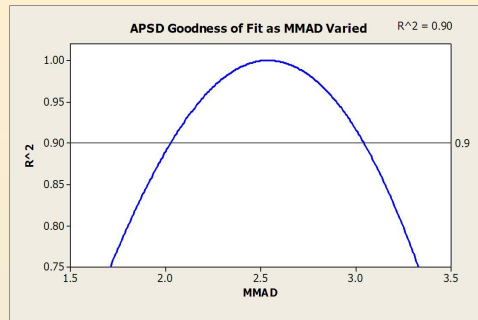
- Two strategies currently being explored
- Strategy A, Limits for Ratio and Grouped Stages Derived Independently from Real Results, OCCs Derived from Model APSDs
- Strategy B, Assumed Method Variances, Common MMAD Requirement Driving Limits for Ratio and Grouped Stages
- The limits used here are selected only to evaluate the test, not the product.

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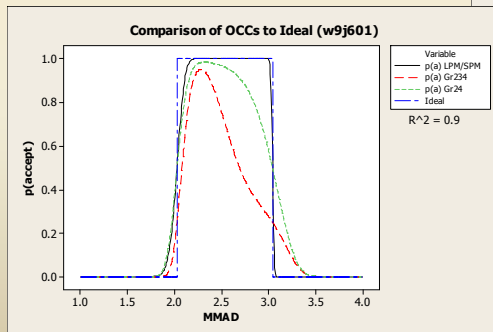
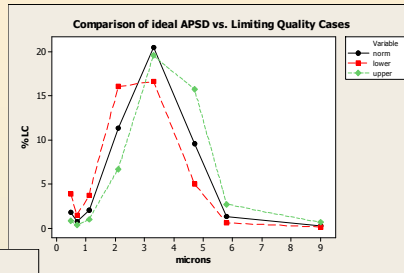
Strategy B

- Determine best fitting continuous APSDs to average stage by stage data for a series of products (8 used in previous publications)
- Construct family of APSD where deliberate change is introduced (e.g. MMAD varied, second mode introduced)
- Assume limits for allowed change to APSD
- Construct OCCs for EDA versus grouped stages based on assumed variability for the respective measurements



Resulting OCCs for w9j601

Illustration of assumed limiting quality cases that define limits used for comparing OCCs ($2.0 < \text{MMAD} < 3.0$)



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

Acknowledgements

- IPAC-RS Board and Member Companies for overall support of this working group
- Dagny Cooke (Ridgefield High School) for help with the OCC work

**IPAC-RS Satellite Conference
at RDD Europe 2011**

**Perspectives on Efficient Data
Analysis Methods and
Abbreviated Impactor
Measurements as Quality
Assessment Tools**

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May 6, 2011

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Program

- **Questions & Answers about Technical Aspects of EDA and AIM. Incorporating EDA and AIM into the Development Cycle.** T. Tougas, BI
- **Panel Discussion**
 - J. David Christopher, M.S. Merck Research Laboratories, Kenilworth, NJ, USA
 - William Doub, Ph.D., US FDA, St. Louis, MO, USA
 - Volker Glaab, Ph.D, Boehringer Ingelheim, Ingelheim, Germany
 - Jolyon P. Mitchell, Ph.D., Trudell Medical International, London, Ontario, Canada
- **Pharmacoepial Perspectives on EDA and AIM - European Viewpoint**
 - Steven C Nichols, Ph.D., Scientific Consultant, Smallwood, Cheshire, United Kingdom representing European Directorate Quality of Medicines (EDQM) Inhalanda Working Party.
- **Pharmacoepial Perspectives on EDA and AIM - US Viewpoint**
 - Paul Curry, Ph.D., Abbott Laboratories, Chicago, IL, USA representing United States Pharmacopeia General Chapters, Dosage Forms Expert Committee.
- **European Regulatory Perspectives on EDA & AIM**
 - Marjolein Weda, Ph.D., National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands.
- **USA Regulatory Perspectives on EDA & AIM (via Teleconference)**
 - Prasad Peri, Ph.D., Food & Drug Administration, Silver Spring, MD, USA.
- **Remarks and Future Directions**
 - Terrence P. Tougas, Ph.D., Boehringer Ingelheim, Ridgefield, CT, USA

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The End

