



International Pharmaceutical Aerosol Consortium on Regulation and Science

<http://ipacrs.com>

**SUMMARY OF DISCUSSIONS AT THE  
IPAC-RS SATELLITE CONFERENCE AT RDD EU 2011  
*PERSPECTIVES ON EFFICIENT DATA ANALYSIS METHODS (EDA) AND  
ABBREVIATED IMPACTOR MEASUREMENTS (AIM)  
AS QUALITY ASSESSMENT TOOLS***

HELD ON MAY 6, 2011 IN BERLIN, GERMANY

This document summarizes discussions at the IPAC-RS Satellite Conference "*Perspectives on Efficient Data Analysis Methods and Abbreviated Impactor Measurements as Quality Assessment Tools*". The conference took place on the afternoon of 6 May 2011, immediately following the RDD-EU 2011 conference. The main RDD program that morning also included four podium presentations by members of the IPAC-RS Cascade Impaction (CI) Working Group, which set the groundwork for the afternoon's discussions; those articles are included in the RDD proceedings:

- **Efficient Data Analysis in Quality Assessment.** Terrence P Tougas. *RDD Europe 2011 (2011), Vol 1, pp 209-214*
- **Detecting Differences in APSD: Efficient Data Analysis (EDA) vs. Stage Grouping** J. David Christopher, Monisha Dey. *RDD Europe 2011 (2011), Vol 1, pp 215-224*
- **Efficient Data Analysis for MDIs and DPIs: Failure Mode Effect Analysis** Volker Glaab, Adrian Goodey, Svetlana Lyapustina, Jolyon P Mitchell. *RDD Europe 2011 (2011), Vol 1, pp 225-236*
- **When Could Efficient Data Analysis (EDA) Fail? Theoretical Considerations** Jolyon P Mitchell, J. David Christopher, Terrence P Tougas, Volker Glaab, Svetlana Lyapustina *RDD Europe 2011 (2011), Vol 1, pp 237-246*

The final program of the Satellite Conference is available online<sup>1</sup> along with the copies of the presented slides<sup>2</sup> (except for Dr. Doub's slides, which were spontaneously volunteered during the discussion). The summary below does not repeat the presentations but focuses on Q&As with the audience. The comments, questions and responses are paraphrased; they are not exact quotes.

**Unless specified otherwise, all speakers and panelists represented their own professional opinions rather than the official positions of the organizations with which they are affiliated**

<sup>1</sup> <http://ipacrs.com/PDFs/CI%20Workshop/CI%20Workshop%20Program.pdf>

<sup>2</sup> <http://ipacrs.com/CI.html>

## Introduction to the Satellite Conference. Technical Aspects of EDA and AIM. Incorporating EDA and AIM into the Development Cycle

Panelists:

**Terrence P. Tougas**<sup>3</sup> (Boehringer Ingelheim, Ridgefield, CT); **J. David Christopher**<sup>4</sup> (Merck, Kenilworth, NJ); **William Doub**, (US FDA, St. Louis, MO); **Volker Glaab** (Boehringer Ingelheim, Ingelheim, Germany); **Jolyon P. Mitchell**, (Trudell Medical International, London, Ontario, Canada)

- *Would we need a separate impactor for each product?*
  - No, we need only a couple of different cut-points for the boundary between large and small particles, because the EDA method is robust with respect to shifts of the boundary (in the studied example, it demonstrated stable performance when the LPM/SPM Ratio was between 0.3 and 3.0). Moreover, all respiratory drugs need to get into the lung, so the sizes of interest will always be around 2-3 microns. Setting the cut-point at a different size (much below or much above 2-3 microns) could be considered if there is an interest in controlling a specific part of the distribution.
- *For solution MDIs, would you require CI data for quality control, or would delivered dose + bulk particle size testing be sufficient?*
  - Solutions are simpler than suspensions. Laser diffraction could be used for sizing droplets. But you still need traceability to the API to satisfy regulatory requirements. For nebulizers, it is possible to build up the traceability chain. EDA can be extended to apply to nebulizers.
- *Can EDA detect if something is wrong with the product, or if it is a wrong product?*
  - Short answer – yes. EDA is an enhancement of the current CI tests. It should be applied only after you have defined the aerodynamic particle size distribution (APSD) of the “right” product. EDA is more sensitive to changes in APSD than current methods, so yes, you will get a signal that something is “wrong” if APSD changes, but you would need to do an investigation, potentially using a full-resolution impactor and/or other tests, to determine the cause. OOS investigations are done in the current system as well.
- *Analysts and managers need to know how to go about using EDA – not just the science and statistics but the practical how-to’s and what’s, so people can get on with it. We are waiting for IPAC-RS to come up with all the answers.*
  - We share this goal. Part of the process of getting there is obtaining feedback from users in settings like this one. We are also developing a book that will set down ‘ground rules’ for EDA and AIM. Members of the European Pharmaceutical Aerosol Group (EPAG) are collaborating with IPAC-RS on the book-writing. In addition, a series of articles has already been published<sup>5</sup>; and more articles are in the works and will be published in due time.

<sup>3</sup> <http://ipacrs.com/PDFs/CI%20Workshop/1-Introduction%20and%20Lifecycle%20-%20Tougas.pdf>

<sup>4</sup> <http://ipacrs.com/PDFs/CI%20Workshop/Detecting%20Differences.pdf>

<sup>5</sup> <http://ipacrs.com/PDFs/Presentations.doc>

- *The LPM/SPM Ratio works like a charm when the cut-off is set at the MMAD. But if you are away from MMAD, the expected ideal Ratio is not 1, so what happens to sensitivity? How far from MMAD could you go?*
  - As long as the LPM/SPM Ratio is within 0.3-3.0, the EDA works. Also, the goal (specification) is not to have the Ratio “close to 1” but close to whatever value you determined during development is typical for your product’s APSD with the chosen boundary.
  
- *Does FDA have any data on the use of EDA or AIM?*
  - [Bill Doub] In my lab, we looked at 4 CFC MDIs and 5 HFA MDIs. There was a 5<sup>th</sup> CFC MDI but it turned out to be expired. We attempted to change their APSDs by introducing an inter-actuation delay, actuator cleaning, and looking at different life stages. We used an Anderson Cascade Impactor (ACI) and looked at the fine particle dose as well. The experiments were conducted because patients are complaining about the CFC-HFA difference. Where we saw statistically significant effects with the full resolution cascade impactor (FRCI), we applied EDA to see if that method showed similar effects. Although the EDA data has not yet been internally validated, qualitatively we saw the same types of APSD changes as were observed using the FRCI. Quantitatively, changes were greater with EDA although RSD was also higher with EDA. For example, effect of cleaning was 4%-11% from FRCI data and 24% for EDA. The effect of delay was 8% with FRCI and 21% with EDA. All LPM/SPM Ratios were 0.2-0.3, so we were probably pushing the limits of sensitivity of EDA. MMADs were 2.2-2.9 microns, and the LPM-to-SPM boundary was set at 2.1 microns.
  
- *If the Ratio is more sensitive than stage groupings, could it be used to predict MMAD?*
  - The Ratio is more sensitive to change. But if you want to predict MMAD, it’s better to calculate MMAD from the full resolution impactor, using an appropriate method (e.g., probit). Incidentally, the USP method for MMADs assumes a long-normal distribution, which is not always valid, and leads to a biased assessment of MMAD<sup>6</sup>. In addition, it is important to look at the entire collection efficiency curve for a most accurate MMAD assessment. For an NGI, we still need a better understanding of collection efficiency curves.
  
- *Does it matter if the impactor is based on viable vs non-viable type?*
  - Those differences can become an issue. Computer simulations could be used to understand the differences between specific platforms.

---

<sup>6</sup> Generalized Simplified Approaches For MMAD Determination. David Christopher, Monisha Dey, Lana Lyapustina, Jolyon Mitchell, Terrence Tougas, Mike Van Oort, Helen Strickland, Bruce Wyka. *USP Pharmacopeial Forum 36(3)*, pp 812-823. May – June 2010

- *As an intermediate step before going to an actual AIM apparatus, could you do a consolidated extract from a group of stages?*
  - Yes, you could do EDA from the full-resolution data, and you could pool the material from several stages by washing them together. Although while you are still in development, you may not know which stages to group yet. And from the time- and resource perspective, it would not be much different than collecting and measuring stages individually, and then adding up the numbers.
  
- *The 1998 draft FDA guidance for MDIs and DPIs requires a +/-15% specification on the mass balance from CI measurements. How will it be done with EDA?*
  - With EDA, besides the LPM/SPM Ratio, the Impactor-Sized-Mass (ISM) needs to be controlled. We are not discussing in detail the performance of the ISM portion of the EDA approach because it will be the same as with the full-resolution and AIM. The ISM gets at some of the mass balance but not all (not the non-sizable portions). However, the delivered dose uniformity (DDU) test, which is also required for these products, does control for the total emitted dose, and in a much more accurate way than current CI measurements on multi-stage impactors. The IPAC-RS position has always been that mass balance should be used as a 'system suitability' indication, not a specification. But your actual regulatory requirement needs to be discussed with the FDA. We have also presented a poster at DDL 2010 about a dual-use DDU/APSD apparatus. If such an apparatus is ever materialized, it could provide a single measurement that would replace both the current DDU and CI tests.
  
- *Air flow recommended for ACIs are 60 L/min and 28.3 L/min. If we want to match the full-stage ACI at 15 L/min, how can we do that? How would AIM measure at low flow rates?*
  - I would like to see calibration data first. Full resolution can measure at 15 L/min but I have not seen it, nor have I seen calibration data for ACI for 28.3 L/min. Before we go forward with ACI, we need reliable data. Currently we are relying on old data from the back of the manufacturer's manual. ACI used to be made of aluminum, but it erodes. Now ACIs are made of steel, and we need new data. I would like to see that gap filled.
  
- *The purpose of using AIM is two-fold: (1) development/characterization; and (2) quality control. Do you plan to publish all the substantiating information, or would it be up to each company to cross-validate to existing impactors?*
  - We need to let things get tested by time and experience. If it takes too long to get these ideas through to USP & EP, then each company should start cross-validating these methods themselves.
  
- *Would AIM and EDA be mandatory or optional?*
  - We thought of them as an alternative for the QC testing, and as an enhancement for development. The use of these or any other methods is of course optional.

## Pharmacopeial Perspectives on EDA and AIM - European and US Viewpoints

Panelists:

**Steven C. Nichols** (Scientific Consultant, Smallwood, Cheshire, United Kingdom representing European Directorate Quality of Medicines (EDQM) Inhalanda Working Party)<sup>7</sup>

**Paul Curry** (Abbott Laboratories, Chicago, IL, USA representing United States Pharmacopeia General Chapters, Dosage Forms Expert Committee)<sup>8</sup>

Dr. Nichols' and Dr. Curry's slides summarized the issues that need to be addressed before AIM and EDA concepts can be included in the pharmacopeias.

- *We don't want to buy new equipment. We suggest that you publish the principles but not specify equipment in EP and USP.*
  - Some apparatus needs to be described in the Pharmacopeia, for regulatory purposes.
- *In the EP, we have NGI family of apparatus. Why not have the NGI concept in USP? We also need to re-think the utility of a twin impinger. It has a role to play, because of the bouncing issues with other cascade impactors.*
  - This topic deserves consideration.
- *Why can't pharmacopeias write requirements for an apparatus, without specifying the apparatus? For example, if USP is moving towards QBD approaches, why do we need to put apparatus description into USP?*
  - Someone needs to be able to go and test the product. Regulators need standard principles, stage cut-offs, validation information, etc. Even now the EP states that you can use ANY method as long as it's validated. But there are legal reasons for describing a specific apparatus. To change that requirement, at least in Europe, someone would need to change the law. If there is enough interest, IPAC-RS and EPAG should develop a proposal/monograph and send it to the EP Inhalanda Working Party for consideration. And since the USP/EP harmonization takes 7 years on average, it would be good to submit the proposed monograph to the USP and EP simultaneously. PharmEuropa can publish your proposal. If you don't come up with a monograph, the EP Working Party will develop one itself, and it may not be exactly what you want to see. Someone also should compare the FPD requirement with the EDA approach.

---

<sup>7</sup> <http://ipacrs.com/PDFs/CI%20Workshop/2-CI%20Workshop%20-%20Nichols.pdf>

<sup>8</sup> <http://ipacrs.com/PDFs/CI%20Workshop/3-CI%20Workshop%20-%20Curry.pdf>

## European and USA Regulatory Perspectives on EDA &amp; AIM

Panelists:

**Marjolein Weda** (National Institute for Public Health and the Environment, Bilthoven, Netherlands)<sup>9</sup>**Prasad Peri** (USA Food & Drug Administration, Silver Spring, MD)<sup>10</sup> - by phone

- *Can you comment on the pharmacopeial discussion?*
  - [M. Weda] Full resolution impactor is needed in the EP for characterization purposes. For quality control, you could remove some stages. Introducing changes to Ph.Eur. quality control methods is allowed and, for example, already happens frequently in HPLC methods (using different columns).
- *If EDA provides better discriminating power, what is the expected sample size?*
  - [P. Peri] We first need to see the data that it indeed provides better discrimination. If this is demonstrated, and if it is validated, FDA would support the use of EDA. The data we have seen so far looks promising, and we'd like to move forward.
- *Would APSD be needed as a release test with the quality-by-design (QBD)?*
  - [P. Peri] If you can correlate APSD to some "in-process" measurement, I personally would support that approach instead of doing end-product testing. The more knowledge and process control, the better assurance that the final product will meet quality requirements.
- *On the statistical issue, and your comment that with two parameters there might be a loss of information: Since these two metrics are capable of discriminating and detecting changes while collecting fewer numbers on a routine basis – that is the whole point. If we could miraculously find a single metric that could control APSD, that would be better still. You need all possibly relevant information in development, but once you have characterized the product and established controls, you shouldn't need to accumulate as many numbers as possible.*
  - [P. Peri] The only two metrics in the EDA approach are ISM and LPM/SPM. If you can show that these give better assurance, discrimination, detection that your product is changing over time, then we would consider it favorably. Right now we do not have the complete data. Papers are being published, presentations are made at meetings, and this knowledge base should continue to build up. We want to encourage better analytical methods and better methodologies. We don't want to hamper progress and innovation.
- *Would FDA require demonstration of the **same** performance between EDA and the current approaches, or **better** performance?*
  - [P. Peri] It can be the same statistically but better in terms of labor, environmental impact, etc.

<sup>9</sup> <http://ipacrs.com/PDFs/CI%20Workshop/4-CI%20Workshop%20-%20Weda.pdf>

<sup>10</sup> <http://ipacrs.com/PDFs/CI%20Workshop/5-CI%20Workshop%20-%20Peri.pdf>

- *What upcoming guidance documents should we expect to see soon?*
  - [M. Weda] Currently there are no concrete plans to update the EMA guidance. If the AIM & EDA topic moves forward, however, EMA/CHMP could decide to re-open the guidance or to provide clarification and additional information via a Q&A.
  - [B. Doub and P. Peri] Work on the new guidance is ongoing. We have another internal FDA teleconference coming up regarding the guidance. But even the current draft MDI/DPI guidance from 1998 does allow alternate approaches. So even if the guidance did not change, you could propose to use AIM and EDA in your application. We want a less prescriptive guidance, but you don't have to wait for it. We might update the guidance with alternative methods. Now the document is in the process of being updated. There is a working group within FDA, which has been working for the past six months, and it will likely be a few more months. It is a slow process, with the writing and other steps. What specifications/limits would you envision for EDA? For example, would you set a range on the Ratio?
    - ◇ [T. Tougas] This is a big dilemma - what should be the basis for setting specifications. Dr. Peri's slides include "typical ranges" for stage groupings – we could use those as a basis, and translate them into the EDA specifications. Ideally, specifications should be tied to clinical performance but in the absence of a quantitative IVIVC, or something else that links in-vitro and clinical performance, we have to go with what has been required historically.
    - ◇ [M. Weda] Why not use development batches' data to set specifications?
    - ◇ [T. Tougas] That would be setting specifications based on capability rather than QBD. From the engineering perspective, that would be a poor way to set specifications. Today's limits are based on process capability, but there is limited experience/data at the time of registration. This results in a band that is too tight for real commercial processes. We can look at the data and use it as a rough guide regarding expected performance and standard deviation, but the modern engineering thought around "capable process" recommends a different approach (e.g., +/- 6 sigma, instead of +/- 3 sigma). Currently in the pharmaceutical industry, if a sponsor does a good job developing a product with a tight distribution, that sponsor will be penalized with very tight specifications. This is counter to the spirit of continuous improvement.

All panelists and audience thanked each other for the productive and informative discussion.

If you have any questions, please contact the IPAC-RS Secretariat at [info@ipacrs.com](mailto:info@ipacrs.com)