Update from Cascade Impactor Working Group for the IPAC-RS/RDD Joint Symposium (April 2020)

Adrian Goodey, J. David Christopher, Terrence Tougas, Rajni Patel, Stephen Stein, Bill Doub, Nicholas Scott, Jolyon Mitchell, Svetlana Lyapustina

BACKGROUND

The Cascade Impactor Working Group (CI-WG) has been in existence for more than fifteen years. Its purpose is to provide a forum for member companies to address specific technical aspects relating to the use of the multi-stage cascade impactor primarily in the context of inhaler product quality control. It comprises a mixture of company representatives and at present has three scientific adviser members, who can offer expertise in specific areas of cascade impacror use.

This WG has had a remit for several years to provide educational materials both to the member organizations as well as externally through the IPAC-RS public access portal. In this context, it has developed a series of on-line instructional tutorials including basic impactor operation, the abbreviated impactor measurement (AIM) and effective data analysis (EDA) concepts the latter two having been conceived and developed by the CI-WG.

A further important role for the CI-WG is that of expert evaluation of regulatory draft guidance documents from the USFDA and the EMA and monographs and chapters intended as official text in the Unitied States and European Pharmacopeias.

Finally, members of the WG have published many peer-reviewed articles relating to their work in archival journals, principally *Journal of Aerosol Medicine and Pulmonary Drug Delivery* and one of the journals of the American Association of Pharmaceuticsl Scientists (AAPS), *AAPS PharmSciTech.*

ACTIVITIES IN 2018-2020

1: JOURNAL ARTICLE:

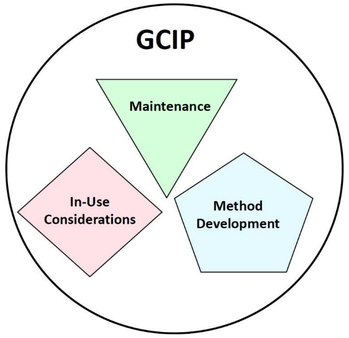
Determination of Passive Dry Powder Inhaler Aerodynamic Particle Size Distribution by Multi-Stage Cascade Impactor: International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) Recommendations to Support Both Product Quality Control and Clinical Programs

Mitchell JP, Stein SW, Doub W, Goodey AP, Christopher JD, Patel RB, Tougas TP, Lyapustina S

AAPS PharmSciTech: 2019;20(5):206.

Content

- Role of the CI in the Pharmacopeial Compendia
- Impactor Selection
- Roles of additional Components
  - Pre-separator
  - Flow Controllers and Related Equipment
  - Flow Rate Stability and Sample Volume
- Enhancements to the CI Method to Support the Clinical Program
- Good Cascade Impactor Practices (GCIP)



2: JOURNAL ARTICLE:

Addressing the Need for Controls on Particle Bounce and Re-entrainment in the Cascade Impactor and for the Mitigation of Electrostatic Charge for Aerodynamic Particle Size Assessment of Orally Inhaled Products: An Assessment by the International Consortium on Regulation and Science (IPAC-RS)
Doub W, Stein SW, Mitchell JP, Goodey AP.
AAPS PharmSciTech. in review at journal.

Content

- Particle Bounce
  - Fundamentals
  - Use of Coatings to Mitigate Particle Bounce on Particle Collection Surfaces
  - Influence of Particle Loading on Particle Bounce
  - Losses to the Internal Walls of the Impactor
  - Particle Bounce in Abbreviated Impactor Measurements
  - Use of Induction Port Coatings to Mitigate Particle Bounce
  - **Particle Bounce/Re-entrainment: Recommendations**
- Electrostatic Charge Effects
  - Mechanisms for Charging Inhaer-Generated Aerosols
  - Charge Acquisition of APIs Upon Interaction with Various Surfaces
  - Factors Influencing Charge Acquisition for pMDI Sprays
  - Factors Influencing Charge Acquisition for DPI Aerosols
  - Influence of Electrostatics on APSD Measurements
  - European Pharmaceutical Aerosol Group (EPAG) Survey of Methods to Mitigate Electrostatic Charge Associated with OIPs
  - **Electrostatic Charge Mitigation: IPAC-RS Recommendations**

air flow control: ±5%
- calibration
- setting
- leakage

environmental: ±5%
- T & RH
- electrostatic charge
- coating on collection surfaces

geometry: ±1%
- nozzles
- induction port

wall/internal losses ±2%

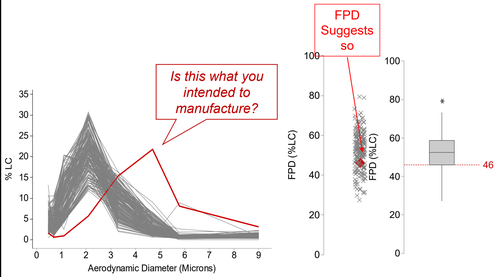
assay variability (API recovery and method variability) are also contributing factors

3: INVITED PRESENTATION AT DRUG DELIVERY TO THE LUNGS-2018:

Cascade Impaction Testing and Data Analysis: Regulatory and Pharmaceutical Developments
Goodey AP. and Mitchell JP.

Content

- How bad is Fine Particle Dose < 5 µm aerodynamic diameter by itself as a measure of inhaler product quality in terms of emitted aerosol aerodynamic particle size distribution (APSD)?
- The benefits of Efficient Data Analysis (EDA) which relies on two independent metrics (Impactor Sized Mass and the Ratio of Large-to-Small Particle Mass) as an Alternative Strategy
- Role of Internal Open (Dead) Volume in Flow Rate Rise Profiles Associated with DPI Testing



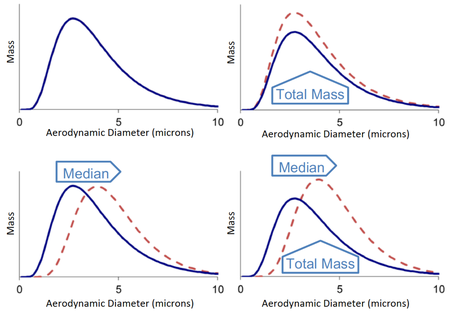
4: FIRST OT THREE ARTICLES FOR *INHALATION* MAGAZINE, COVERING THE LIMITATIONS OF EXISTING METHODS FOR CHARACTERIZING INHALER APSD BY CASCADE IMAPCTOR:

The liability of relying on the fine particle dose (FPD) metric for quality control

Goodey AP, Mitchell JP, Doub W., Christopher, JD
Inhalation: April 2020

Content

- Identifying the liability of relying on FPD alone, by means of example APSDs from the IPAC-RS database
- Understandling why FPD alone fails as a product quality control metric
- Context in relation to shifts in mass median aerodynamic diameter (MMAD) of the underlying APSD
- Implications



An APSD has two orthogonal dimensions: mass and size. For quality control of the APSD of an OIP, the testing and metrics must be sensitive to changes in both dimensions

Parts 2 and 3 to Follow:

Part 2: The Limitations of Impactor Stage Groupings for Characterizing Inhaler APSD

- Tentative publication in August 2020

Part 3: How Efficient Data Analysis Provides a High Quality Diagnostic of Product Quality in Relation to the Underlying Emitted Aerosol APSD

- Tentative publication in December 2020

OTHER ACTIVITIES

- **CONTRIBUTOR TO THE IPAC-RS RESPONSE TO THE FDA DRAFT REVIEWER GUIDANCE 'METERED DOSE INHALER (MDI) AND DRY POWDER INHALER (DPI) PRODUCTS: QUALITY CONSIDERATIONS (April 2019)**
- **CONTRIBUTOR TO THE IPAC-RS RESPONSE TO USP CALL FOR PUBLIC REVIEW FOR REVISED CHAPTER <601> 'Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests' published in *Pharm. Forum* 2018; 44(5)**
- **CONTRIBUTOR TO THE IPAC-RS RESPONSE TO USP CALL FOR PUBLIC REVIEW FOR REVISED CHAPTER <601> 'Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests' published in *Pharm. Forum 2019; 45(6)***
- **CONTRIBUTOR TO THE IPAC-RS RESPONSE TO USP CALL FOR PUBLIC REVIEW FOR CHAPTER <1603> 'Good Cascade Impactor Practices' published in *Pharm. Forum 2019; 45(2)***
- **CONTRIBUTOR TO THE IPAC-RS RESPONSE TO USP CALL FOR PUBLIC REVIEW FOR CHAPTER <1604> 'Data Interpretation of Aerodynamic Particle Size Distribition Measurements for Orally Inhaled Products' published in *Pharm. Forum 2019; 45(2)***

CONCLUSIONS

The Cascade Impactor WG continues to add value to the overall efforts the IPAC-RS organization to improve the science knowledge base in association with the development and quality control of orally inhaled and nasal products.

In particular, the acceptance of the abbreviated impactor measurement (AIM) and Efficient Data Analysis (EDA) concepts as well as the development of robust methods involving the cascade impactor that are more clinically appropriate, are foreseen as priority topics for the immediate future.

ACKNOWLEDGEMENTS

The authors would like to thank the IPAC-RS Board of Directors for its support of this project.

Corresponding Author: Jolyon P. Mitchell (mitchelljolyon@gmail.com)