# Lost in Terminology!!

## EPAG encourages Harmonization of Quality Attributes of Inhalation Products in International Pharmacopeias, Regulatory Guidelines and Literature

Christel Schmelzer [1], Caroline Dick [2], European Pharmaceutical Aerosol Group

[1] Boehringer Ingelheim Pharma GmbH & Co KG, D-55216 Ingelheim, Germany, [2] Vectura Limited, One Prospect West, Chippenham, Wiltshire, SN14 6FH, UK

EPAG
European Pharmaceutical Aerosol Group

## INTRODUCTION

There are currently wide differences in the use of attributes describing the **quality of inhalation** drug products in literature and by companies and international regulatory guidance like

- international pharmacopeias [1, 2],
- various regulatory guidance from FDA, EMA and Health Canada [3, 4, 5, 6],
- ICH guidelines [7] and ISO standards [8].

Different terms for the same quality attributes were collected from the various sources to make the broad variety visible.

European Pharmaceutical Aerosol Group (EPAG) presents a **survey** of most commonly used terms for quality attributes by the member companies and proposes harmonization in regulatory guidance and communication.

## MATERIALS AND METHODS

The pharmacopeias, guidance and guidelines were systematically screened by the author for their quality terms for inhalation drug products. These were **descriptive quality terms** as well as terms required as **testing parameters** for quality attributes of **one time characterization studies** or **routine quality testing**.

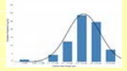
- The found terms were grouped according to their use and listed together with their source in tabular lists (for colors see reference list).
- Each EPAG indicated all the terms in the list that it uses with a number randomly dedicated to this company* (e.g. 1) and introduced and marked respectively all additional terms it uses in its internal and external regulatory submission documents.
- Some EPAG companies involved their development-, analytical-, quality- or regulatory affairs departments.
- **17** (about 3/4) of the 23 EPAG member companies responded (below **bolded**).

## RESULTS

*** Each EPAG member company was given a dedicated random number**

### PSD

| Example Terms | Source | EPAG company using this term* |
|---|---|---|
| Aerodynamic assessment of fine particles | EP | |
| Aerodynamic particle size distribution (APSD) | FDA | 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 14, 15, 17 |
| Aerodynamic size distribution | USP | |
| Aerosol | EMA USP | 2, 5, 15, 17 |
| Deposition of Emitted Dose (DoED) | | |
| Fine particle characteristics | EP | |
| Group emitted mass | | |
| Multi-point particle size test | EMA | |
| Particle size | ICH EP USP | 2, 15 |
| Particle Size Distribution | ICH FDA | 14, 15, 17 |
| Particle Size Distribution (of the delivered dose) (PSD) | EMA EP | 5, 8, 15 |
| Particle Size Distribution of Emitted Dose | FDA | 12, 15 |
| Stage groupings | | 2, 6, 7, 9, 10, 11, 15 |

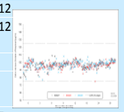


### Mean Dose

| Example Terms | Source | EPAG company using this term* |
|---|---|---|
| Mean delivered dose | EMA | 2, 3, 4, 5, 6, 7, 8, 10, 11, 14, 17 |
| Mean emitted dose | | 9 |

### Dose uniformity

| Example Terms | Source | EPAG company using this term* |
|---|---|---|
| Content uniformity | EMA | 8, 15 |
| Delivered dose rate | EMA | |
| Delivered Dose Uniformity | EMA USP | 2, 3, 7, 8, 11, 13 |
| Delivered Dose Uniformity over Entire Contents | USP | |
| Delivered dose uniformity over patient flow rate range | EMA | 6 |
| Delivered dose uniformity through container life | EMA | 2, 4, 5, 8, 10 |
| Dose content uniformity | FDA USP | 2, 11, 15 |
| Dose content uniformity through container life | FDA | 8, 11, 13 |
| Emitted Dose | | 9 |
| Emitted dose content uniformity | FDA | 12 |
| Emitted dose content uniformity through container life | FDA | 12 |
| Emitted Dose Uniformity | | |
| Emitted Dose Uniformity over Entire Contents | USP | |
| Spray content uniformity | FDA USP | 5 |
| Uniformity of delivered dose | EP FDA | 5, 6, 13, 14 |
| Uniformity of dosage units | ICH | 12, 15 |
| Uniformity of emitted dose | | 9 |



### Source

| Example Terms | Source | EPAG company using this term* |
|---|---|---|
| Environmental moisture | EMA | |
| Moisture content | EMA FDA | 2, 3, 8, 12, 13, 15 |
| Water content | ICH FDA USP | 4, 6, 7, 8, 9, 10, 11, 14, 15 |

### Delivered Dose

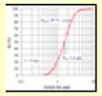
| Example Terms | Source | EPAG company using this term* |
|---|---|---|
| Active substance delivery rate | EP | |
| Delivered dose | EMA EP USP | 1, 2, 5, 8, 9, 10, 11, 14, 15, 17 |
| Delivered dose (at patient interface) | | |
| Delivered dose (ex-valve, ex-delivery device) | EMA USP | 2, 3, 4, 6, 8, 11, 13 |
| Device metered dose | FDA | |
| Discharged dose | FDA | |
| Emitted dose | | 12 |
| Emitted dose at the mouthpiece | FDA | |
| Emitted mass | | 9 |
| Final dose | EMA | |
| Label claim | EMA FDA | 1, 2, 5, 8, 9, 11, 15 |
| Labelled dose | EP USP | 2 |
| Minimum delivered dose | EMA | |
| Minimum dose | USP | |
| Minimum recommended dose | EMA EP USP | 2 |
| Nominal delivered dose | | 10 |
| Pre-dispensed dose | EP | |
| Pre-metered dose | FDA | |
| Target delivered dose | USP | 6, 13 |
| Target emitted dose | | 12 |

### Foreign Particles

| Example Terms | Source | EPAG company using this term* |
|---|---|---|
| Foreign particles | | 2, 4, 9, 10, 11, 15 |
| Foreign particulate matter | FDA | 1, 6, 8, 13, 14, 15 |
| Foreign Particulates | USP | 8, 12, 15 |
| Microscopic Evaluation | FDA | 2, 8, 9, 15 |
| Particulate | | 15 |
| Particulate matter | ICH FDA | 2, 3, 5, 15 |

### Cumulative Particle Size

| Example Terms | Source | EPAG company using this term* |
|---|---|---|
| Cumulative mass undersize a given stage | EMA | 1, 2, 12 |
| Cumulative percentage of delivered mass less than stated aerodynamic diameter | USP | 17 |
| Emitted fraction | USP | |
| Fine Particle Dose (FPD) | EP USP | 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 17 |
| Fine Particle Fraction (FPF) | USP | 2, 3, 4, 5, 6, 7, 8, 10, 11, 13, 17 |
| Fine Particle Mass (FPM) | EMA EP | 2, 3, 6, 8, 9, 11, 12, 13, 14, 15, 17 |
| Fine Particle Mass over patient flow rate range | EMA | |
| Fine Particle Mass through container life | EMA | |
| Geometric Standard Deviation (GSD) | EMA USP | 1, 2, 3, 6, 7, 8, 9, 14, 15, 17 |
| Impactor sized mass | | 9 |
| Mass Median Aerodynamic Diameter (MMAD) | EMA USP | 1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 14, 15, 17 |
| Respirable Fraction (RF) | | 1, 15, 17 |
| Single dose fine particle mass | EMA | 5 |
| Very Fine Particle Fraction (VFPF) | | 17 |



### Shot weight

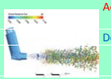
| Example Terms | Source | EPAG company using this term* |
|---|---|---|
| Actuation weight / mass | | 2, 3, 4 |
| Delivered mass / volume | | 5, 10, 17 |
| Emitted mass | | 12, 17 |
| Emitted weight | | 9 |
| Metered mass | | 5, 10 |
| Pump delivery | FDA | 5 |
| Sample weight | | |
| Shot weight | EMA FDA | 1, 2, 6, 7, 8, 11, 14, 15 |
| Uniformity of weight per actuation | EMA | 15 |
| Valve Delivery / shot weight | FDA | 3, 6, 8, 11, 13 |

### Germs

| Example Terms | Source | EPAG company using this term* |
|---|---|---|
| Antimicrobial preservation / preservative | EMA EP | 5 |
| Antimicrobial preservative content | ICH | |
| Antimicrobial preservative effectiveness | ICH | |
| Microbial / Microbiological limits | EMA | 14, 15 |
| Microbial assessment | | 4, 9, 12, 17 |
| Microbial count | EMA | 14 |
| Microbial enumeration tests | EMA | 6 |
| Microbial limits | ICH FDA | 3, 8, 12, 13, 15 |
| Microbial quality | | 10, 11 |
| Microbiological quality | EMA EP | 5 |
| Preservative | FDA | 8 |
| Preservative content | EMA | 5 |
| Preservative effectiveness | FDA | 5 |
| Preservative efficacy | EMA EP | 5, 8 |
| Sterility | ICH EMA USP | 5, 8, 12 |

### Actuation

| Example Terms | Source | EPAG company using this term* |
|---|---|---|
| Actuation | EMA FDA | 2, 3, 4, 5, 8, 11, 12, 13, 14, 15, 17 |
| Deliveries | EP | |
| Dose | EMA EP FDA | 2, 5, 6, 8, 10, 11, 13, 14, 15, 17 |
| Labelled number of actuations | EMA FDA | 8, 15 |
| Last container exhaustion dose | EMA | |
| Last labelled dose | EMA | |
| Metered doses | | 5 |
| No of actuations per container | EMA FDA | 3, 4, 5, 8, 10, 14 |
| No of actuations per inhaler | | 12 |
| No of deliveries per inhaler | EP | 2, 9, 11 |
| Puffs | | 5 |
| Shots | | 11, 15 |
| Tail-off profile | EMA | 7, 13 |



## DISCUSSION AND CONCLUSION

- The purpose of this **survey** among the EPAG member companies is to make the broad variability of terminology for quality attributes of inhalation drug products and inhalers in the guidelines visible (see tables).
- *Find the **complete list** of quality terms on our WEBSITE* www.epag.co.uk
- Companies are not only using the full variety of quality terminology proposed by regulatory guidance for description of quality attributes in submission documentation and communication with regulatory authorities, but in addition, some EPAG companies are using **alternate quality terms**. In some member companies, the terminology for the same drug product and quality attribute even differs for the different regions of submissions.
- This difference in terminology creates a **burden** for internationally operating companies.
- An approximation to **harmonization** of quality attributes for inhalation drug products over all regions of the world would be a valuable goal to achieve for ease of compilation of documentation for international submissions or company internal documents like testing specification for drug products and/or inhalers.
- As a starting point for international attempts to achieve this **harmonization**, we publish this survey.
- **EPAG** encourages **individuals and organizations** that are responsible for the determination of binding terms for inhalation products in pharmacopeias and regulatory guidance to aim for consolidation and harmonization of the terminology in all regions.
- Since the current difference in terminology creates a burden for internationally operating companies, EPAG is more than willing to **support** all attempts that aim for harmonization.

## REFERENCES

**References and hierarchy of colors**

[7] ICH(1999): Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (**ICH**)
[5] European Medicines Agency (2006): EMEA/CHMP/QWP/49313/2005 (CHMP) Guideline on the pharmaceutical quality of inhalation and nasal products (**EMA**)
[6] Health Canada (2006): Guideline on the pharmaceutical quality of inhalation and nasal products
[2] European Pharmacopoeia (2014): 8th Edition (**EP**)
[4] FDA CDER Draft Guidance for Industry (1998): Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products (**FDA**)
[3] FDA CDER Guidance for Industry (2002): Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products (**FDA**)
[1] United States Pharmacopeia (2014): USP36 – NF31 (**USP**)
[8] International Standards Organization (ISO) standards

**EPAG 2014**: 3M, **Actavis, Almirall Sofotec**, **Aptar Pharma**, **AstraZeneca, Bespak Europe Ltd, Boehringer Ingelheim, Chiesi, GlaxoSmithKline**, Hovione, **McNeil AB**, MundiPharma, **Mylan**, **Novartis**, **Pari, Philips-Respironics**, **Prosonix Ltd**, Sanofi, **SkyePharma**, Teva, Trudell Medical International, **Vectura**, **Zentiva Inhalationsprodukte GmbH**