Current EU regulatory requirements

- European Pharmacopoeia (Ph.Eur.)
  - Preparations for Inhalation: using apparatus / procedure C, D, or E described in chapter 2.9.18, calculate fine particle dose
  - Methods of Analysis, chapter 2.9.18, Aerodynamic assessment of fine particles

Fine particle dose = the mass of active substance less than 5 µm (determined with apparatus C, D or E)

Determination of MMAD/GSD not mandatory.
Current EU regulatory requirements (cont.)

- **EMA Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products**
  - **Pharmaceutical development:** Fine particle mass and individual stage particle size distribution
  - **Drug Product Specification:** Fine particle mass, tested with validated multistage impactor or suitably validated alternative

*Fine particle mass* = quantity of drug substance that is generally considered to be of a size capable of penetrating the lung during inhalation (approx. 5 µm and smaller)

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Important to notice:

- **Full resolution data** (individual stage impactor results) required during **development**
- **Reduced data** (fine particle dose) acceptable for **quality control**

- **Ph.Eur. tests not mandatory:** alternative procedures are allowed
Important to notice (cont.):

- Purpose of development: characterisation of \textit{in vivo} test batches and commercial batches
- Purpose of QC-testing: rejecting unacceptable batches

- QC-testing is only one part of the control strategy (a batch will never be accepted on QC-testing only)

Current practice in registration files

- Ph.Eur. method (mostly apparatus/method D or E, sometimes C) is used.
- Individual stage impactor data in section on pharmaceutical development.
- Upper and lower limit for fine particle dose or fine particle mass in Drug Product Specification, based on \textit{in vivo} batches.

Alternative methods have been accepted (Laser Diffraction; LD); correlation between LD results and impactor results was demonstrated; limits for FPD/FPM in Drug Product Specification.
### What would be new?

**Difference in amount of data:**
No full resolution data obtained during QC-testing.

**Difference in apparatus:**
Several impactor stages will be eliminated (but at least for pMDIs the flow rate will remain the same: 28.3 l/min).

**Difference in metrics:**
AIM-EDA will not lead to upper and lower limits for FPD/FPM, but for ISM and ratio LPM:SPM.

### Does this have any consequences?

**Difference in amount of data:**
No full resolution data obtained during QC-testing.

**But:** authorities never see/ask for full resolution data for a commercial batch; the certificate of analysis only mentions the FPD/FPM as required according to the drug product spec;

**Comparable situation:** dissolution testing of tablet; full dissolution rate profile not required for QC; only testing at e.g. timepoint 30 minutes needed according to drug product specification.
Does this have any consequences?

**Difference in apparatus:**
Several impacter stages will be eliminated.

This may have consequences for post-marketing surveillance studies.

On one hand: Official Medicines Control Laboratories (OMCLs) **will be able to test ISM and ratio LPM:SPM (apparatus available) and check compliance with product specification.**

Does this have any consequences? (cont.)

On the other hand: in case of **dispute** the *Ph.Eur. methods* of analysis are alone **authoritative**; this implies that full resolution data will be obtained.

This seems to be **no problem**: ISM and LPM/SPM can be calculated from the full resolution data.

**But:** precision of ISM and LPM/SPM results obtained with complete impacter may differ from those obtained with abbreviated impactor; this may have consequences for accepting / rejecting batches.
Does this have any consequences? (cont.)

**Difference in metrics:**
AIM-EDA will not lead to upper and lower limits for FPD/FPM, but for ISM and ratio LPM:SPM.

Ph.Eur. requires testing of FPD.

Cut-point for LPM and SPM is not necessarily identical to cut-point for FPD. In case of difference: does a correlation exist between FPD and ISM/ LPM:SPM?? If yes, then no problem.

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What are the options to get approval?

**Most optimal solution would be:**
1. Adoption of **AIM-methodology** as option in Ph.Eur. chapter 2.9.18 (with no specific configuration). Harmonize with USP/JP!
2. Inclusion of **ISM** and **LPM:SPM** concept in Ph.Eur. Chapter 2.9.18 (as optional).
3. Amendment of Ph.Eur. monograph on Preparations for Inhalation: deletion of Fine Particle Dose as mandatory test; replace by more general requirement to adopt limits for those parameters that are able to discriminate between acceptable and unacceptable batches.
What are the options to get approval? (cont.)

But: changing Ph.Eur. takes time!!!

Option for amending EMA guideline:

Q&A:

What would be a ‘suitably validated alternative’ to fine particle mass testing with a multistage impactor?

and:

What kind of ‘alternative limits’ for fine particle mass are allowed and what kind of justification should be provided?

Other (less preferable) options:

1. **Simply use only AIM** (no change in metrics) and demonstrate that FPD/FPM obtained with AIM correlates to that obtained with complete impactor.

2. **Use AIM, ISM, LPM:SPM** (obtained with AIM) and **show correlation** with FPD (obtained with complete impactor).

3. Take FPD as cut-off: **SPM=FPD** and demonstrate discriminatory power to detect changes.

4. Adopt limits for ISM and LPM:SPM (obtained with AIM) as well as limits for FPD (obtained with complete impactor), but **notify FPD-test as ‘non-routinely tested’**.
Conclusion

Regulatory acceptance of EDA-AIM would be most appropriately gained by adoption in Ph.Eur.

Use of AIM alone would, under current regulatory requirements, be the most feasible option.

Although still some AIM-EDA issues unclear:
- Suitable for all kinds of inhalation products?
- Flow rates AIM in case of DPIs different from complete impactor?
- ...

the concepts behind AIM-EDA seem rationale and promising......

Thank you for your attention!