OIP development in practice: overcoming barriers to bioequivalence

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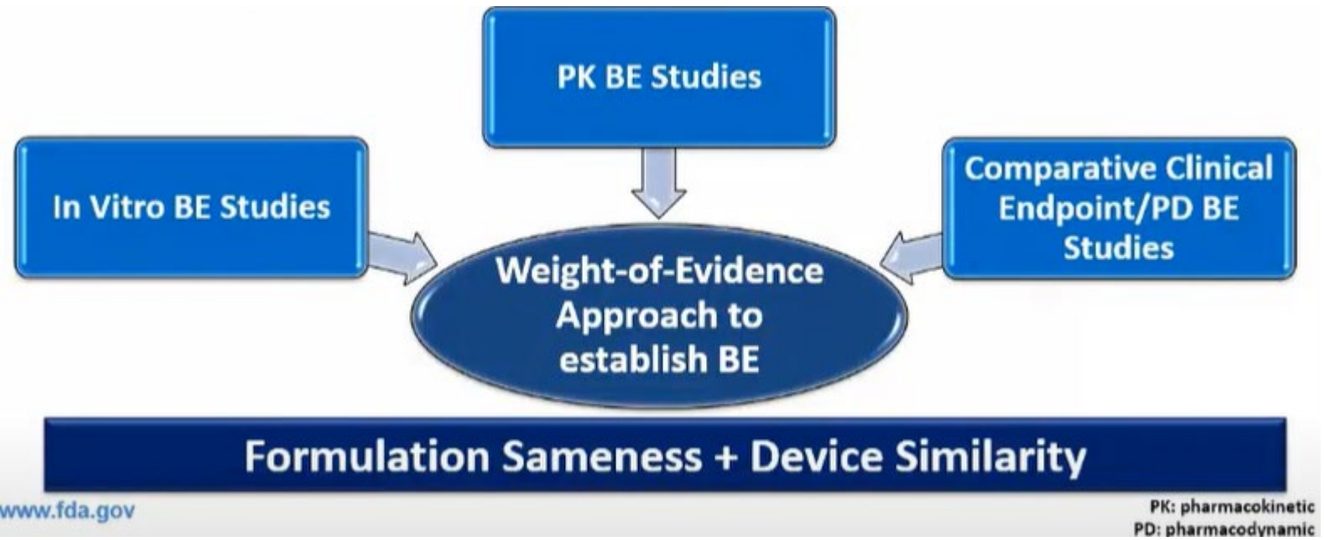
polpharma

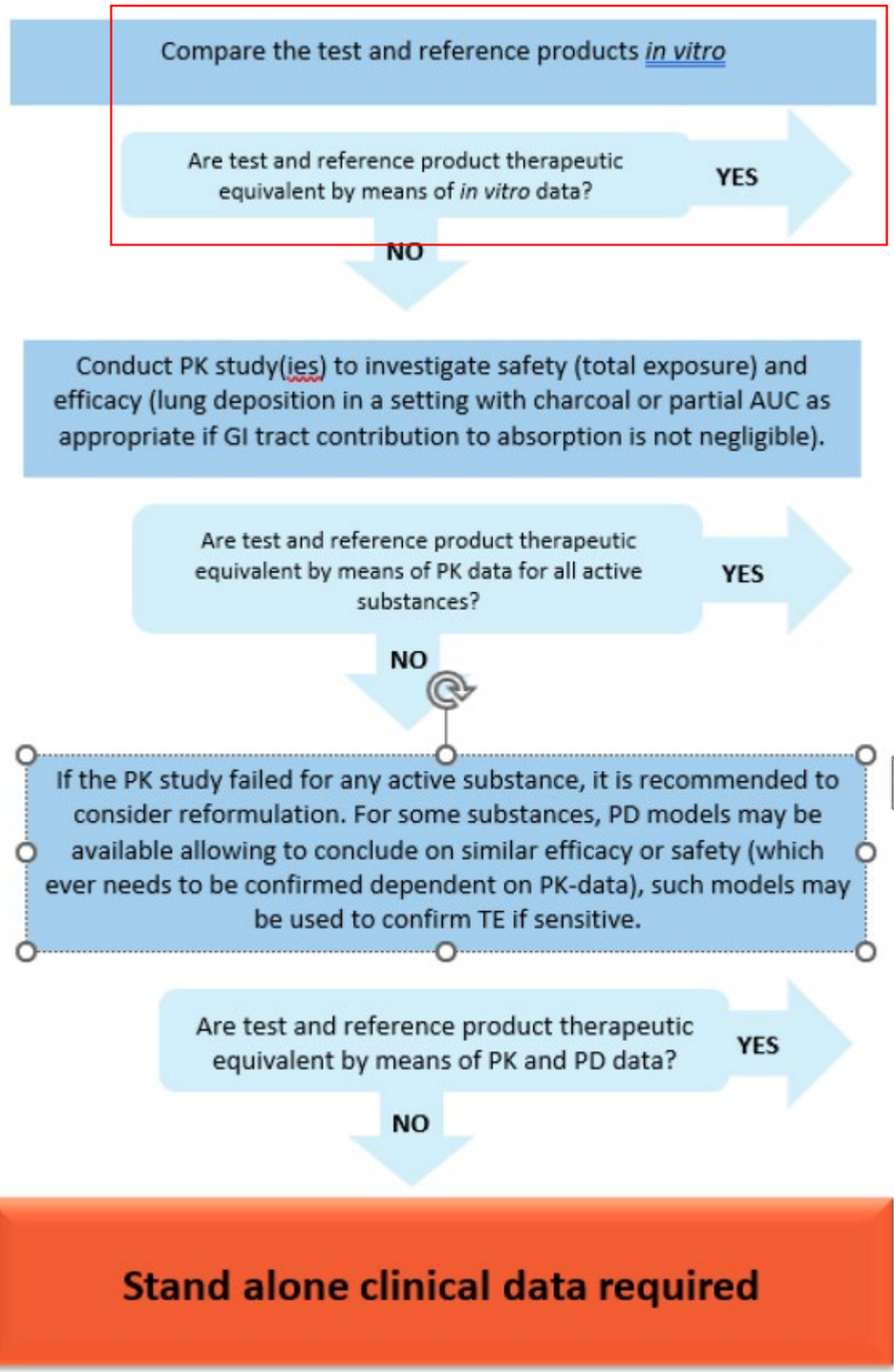
Agenda

- Orally Inhaled Products (OIP) – regulatory framework
- In-vitro Therapeutic Equivalence (TE) – case study
- Updated guidelines – impact on pharmaceutical development and in-vitro approach
- Conclusions

Orally Inhaled Products (OIP) – Regulatory Approach

Weight of Evidence (FDA) vs Stepwise Approach (EMA)





Case study - in-vitro comparison

Generic DPI (1 strength) compared to REF acc. OIP guideline CPMP/EWP/4151/00 Rev. 1 (still in force till 02.2026):

1. *The product contains **the same active substance** (i.e. same salt…)*

→ confirmed, the same salt as REF

2. *The **pharmaceutical dosage form is identical** (e.g. …DPI, etc.)*

→ confirmed, inhalation powder hard capsules (DPI) with co-packaged single dose inhaler device

3. *The active substance is in the solid state: any **differences in crystalline structure and/or polymorphic form** should not influence the dissolution characteristics, the performance of the product or the aerosol particle behaviour*

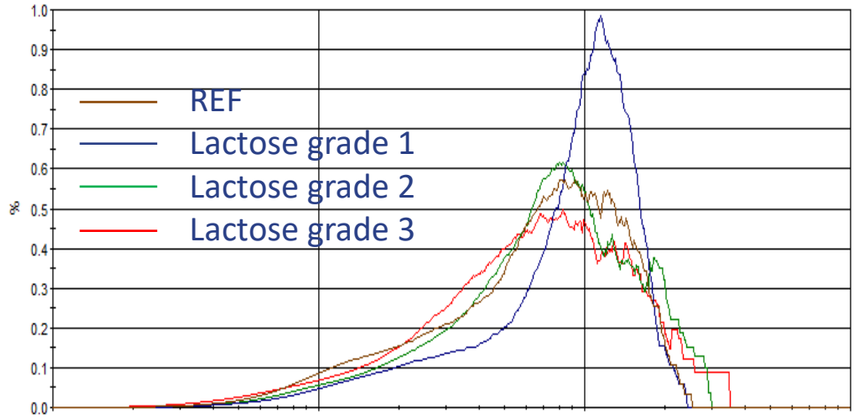
→ single polymorphic form demonstrated, similar DD and APSD

Case study - in-vitro comparison (2)

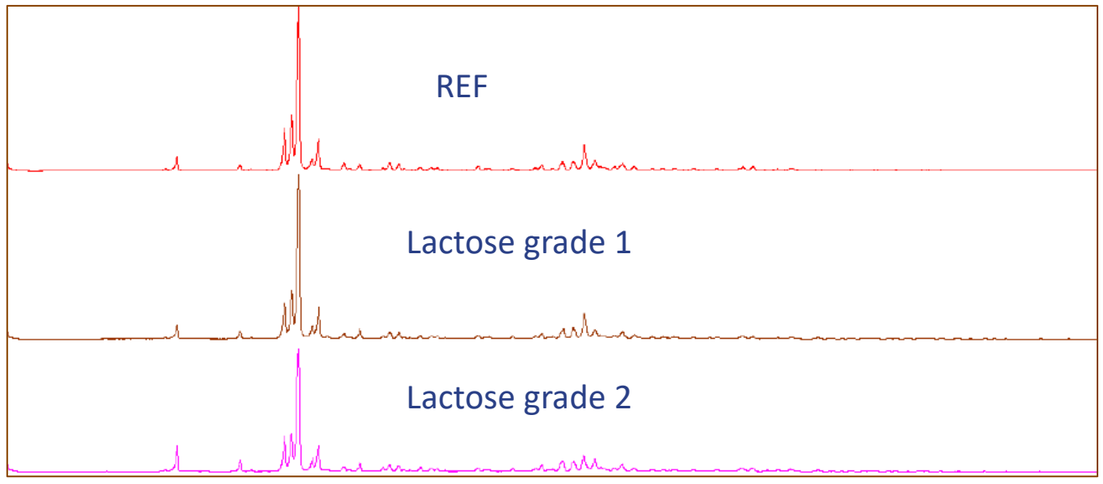
4. Any **qualitative and/or quantitative differences in excipients should not influence the performance** of the product…

- Lactose comprises a major part of the formulation
- The same amounts of lactose as REF (lactose content declared in SmPC)
- Similar grade of lactose as in REF
- Similar XRPD, PSD, DD, APSD etc.

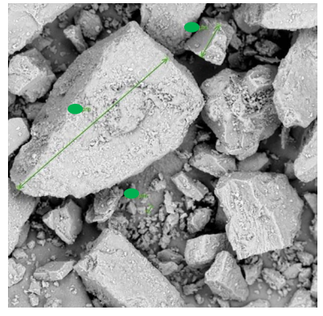
PSD:



XRPD:



SEM:



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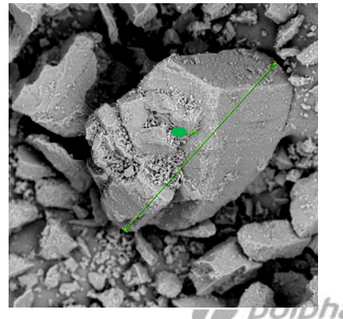


TEST

Case study - in-vitro comparison (3)

5. *Any qualitative and/or quantitative **differences in excipients should not change the safety** profile of the product*

→ No significant differences demonstrated

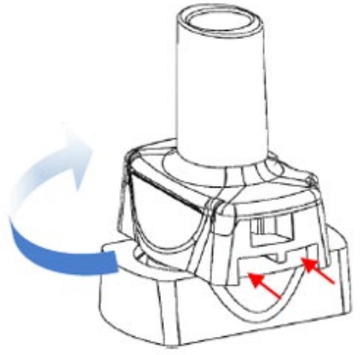
6. *The **inhaled volume through the device** to enable a sufficient amount of active substance into the lungs should be similar (within +/- 15%)*

→ Proposed device with same mechanism of de-agglomeration and equivalent resistance

7. ***Handling** of the inhalation devices for the test and the reference products in order to release the required amount of the active substance should be similar*

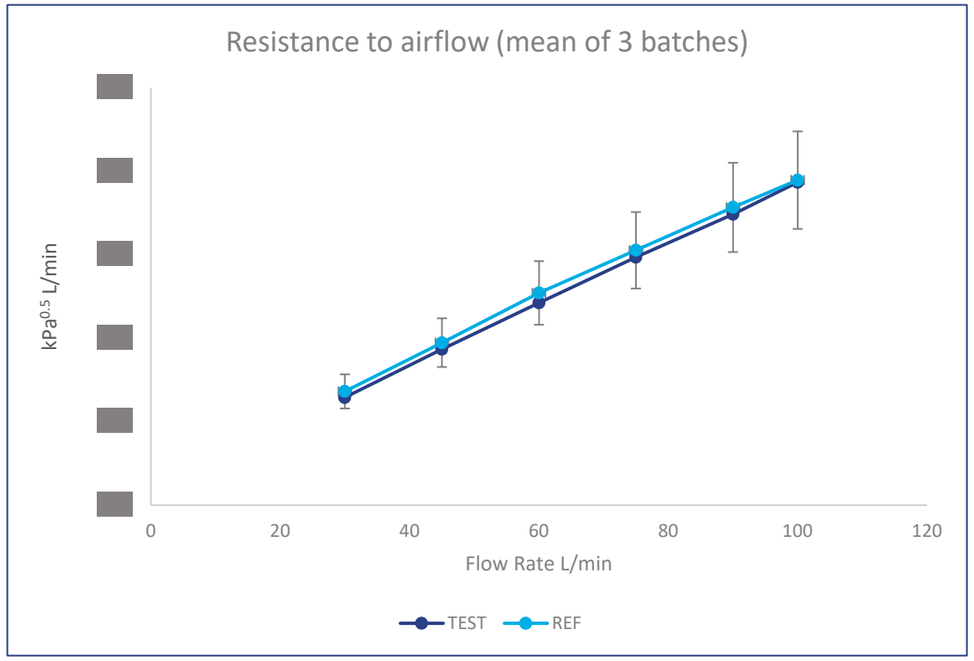
→ Handling similar to REF except for the way the capsule is punctured

→ No impact on DD



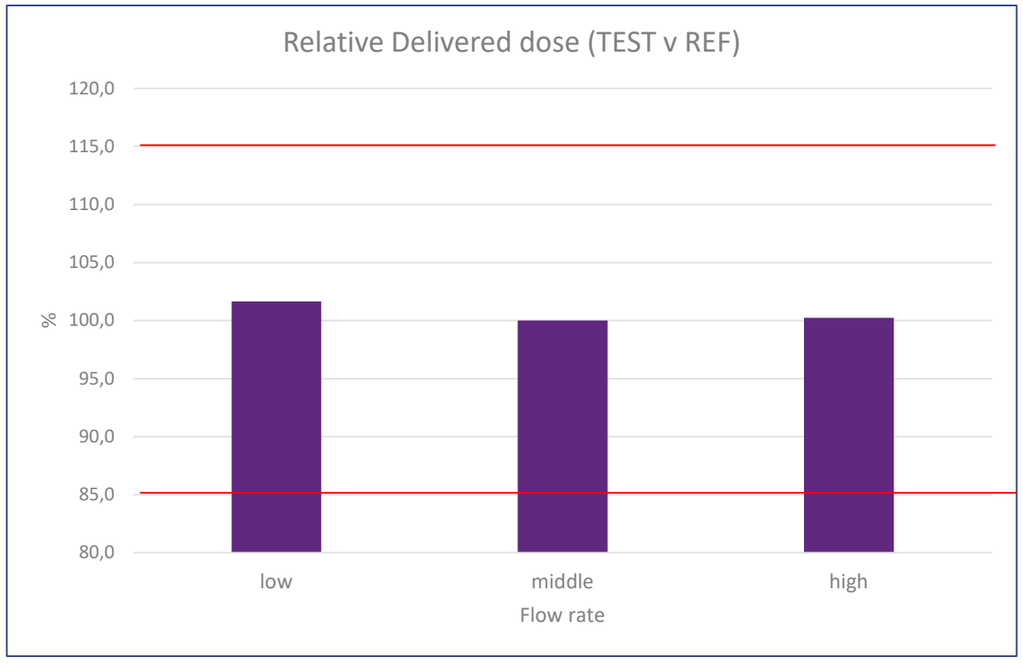
Case study - in-vitro comparison (4)

8. *The inhalation device has the same **resistance to airflow** (within +/- 15%)*



→ Resistance to airflow „sameness” demonstrated

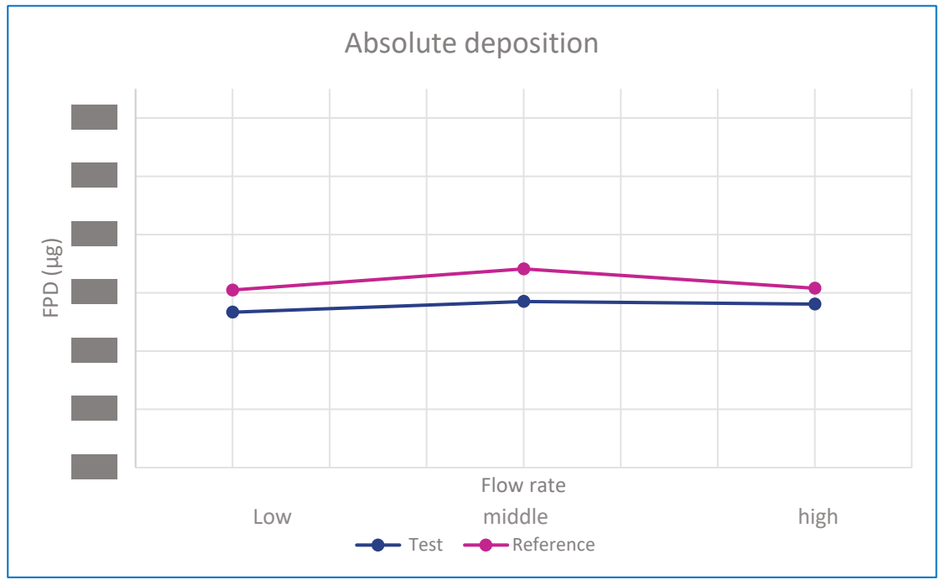
9. *The **target delivered dose** should be similar (within +/- 15%)*

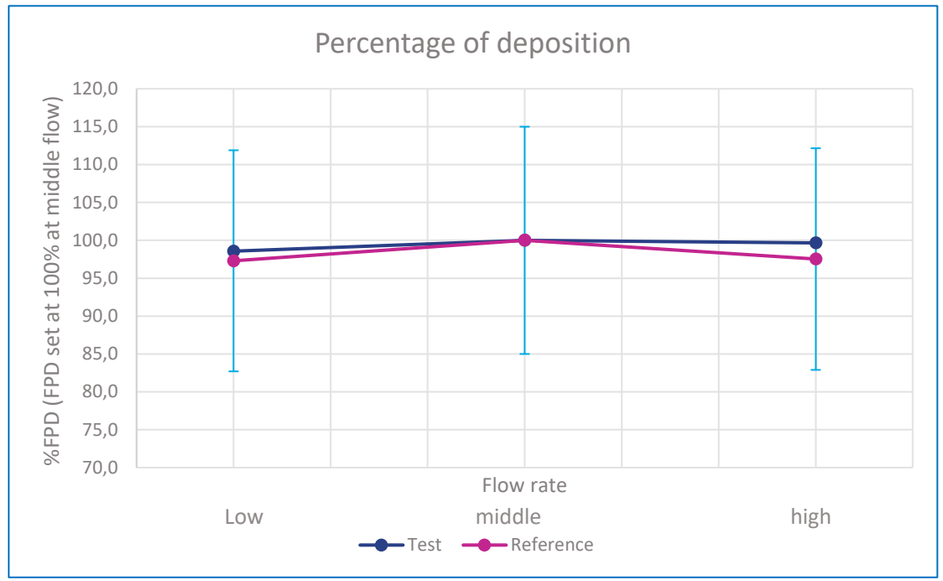


→ Similar DD demonstrated across minimum (10th percentile), median and maximum (90th percentile) achievable flow rate in the target patient population

Case study - in-vitro comparison (5)

Flow rate (FR) dependency of dry powder inhalers



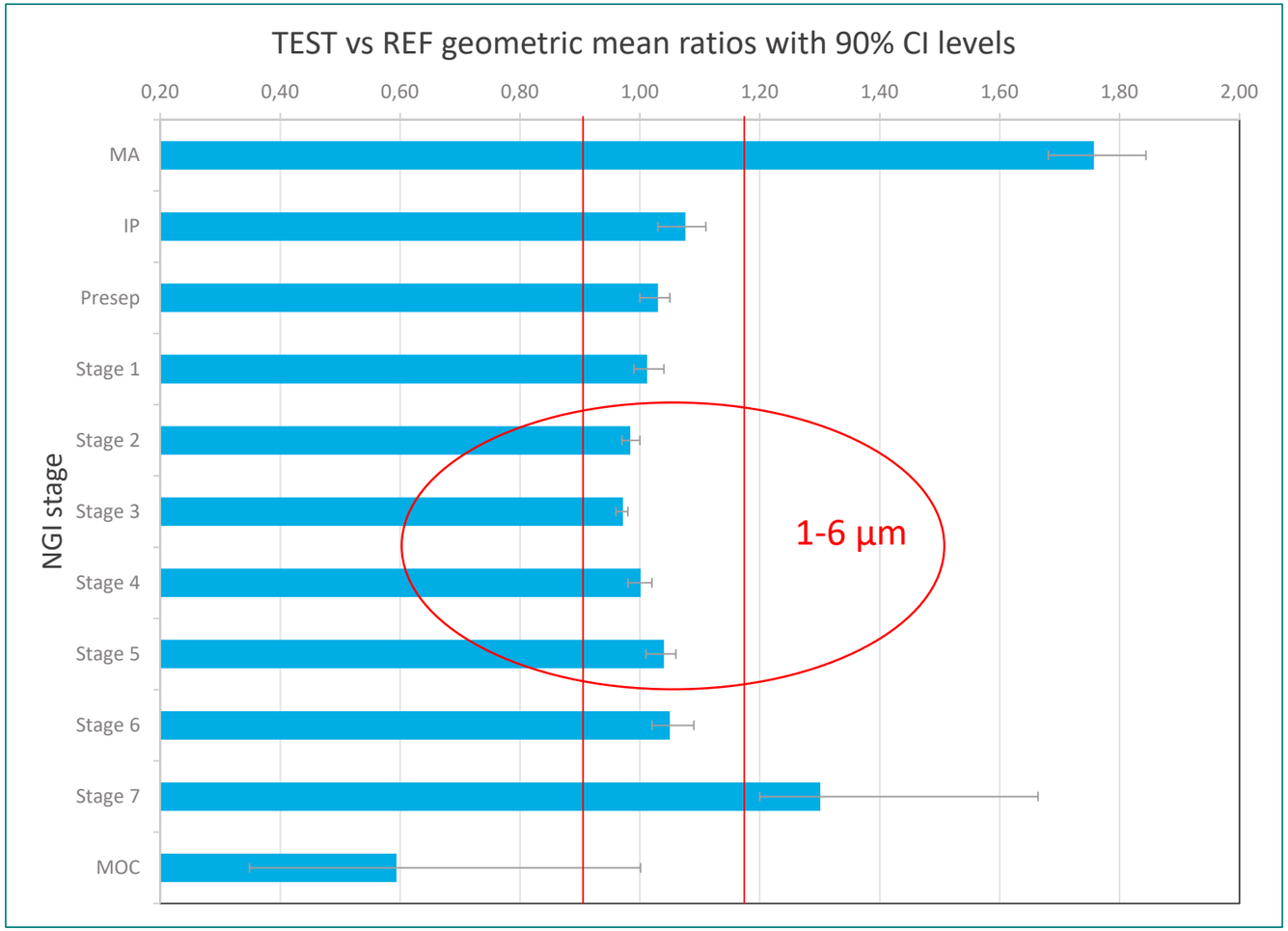


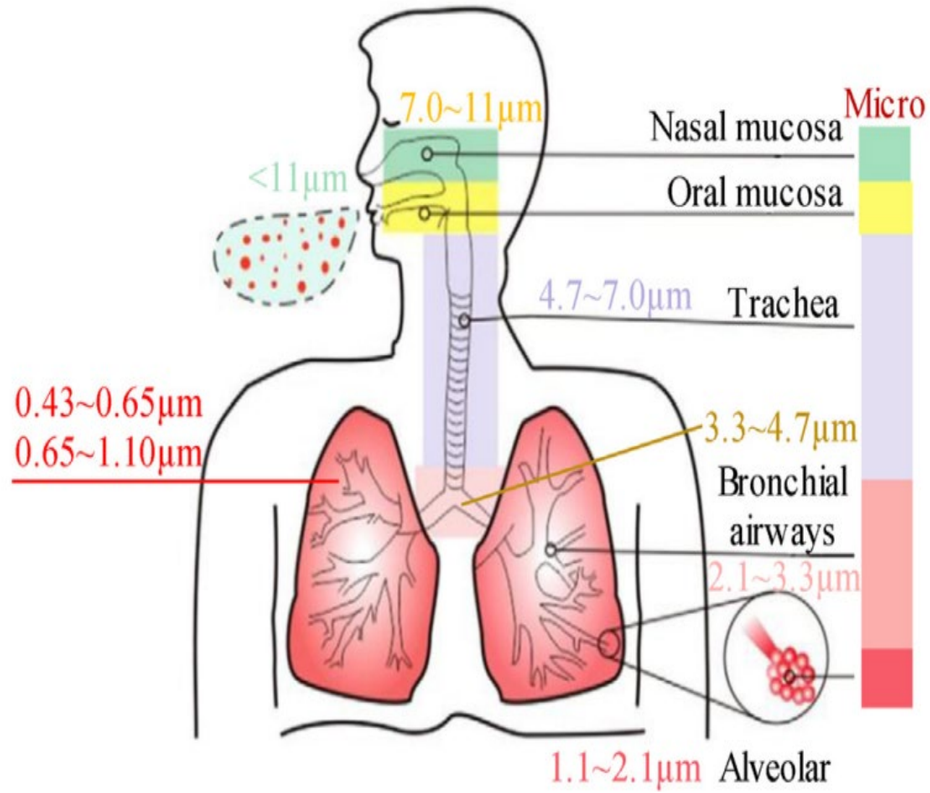
- No FR dependency demonstrated
- Point estimate of FPD of TEST within ± 15% of REF for each tested FR
- PK data (if applicable) can be obtained in healthy volunteers

Case study - in-vitro comparison (6)

*Data from the **complete particle size distribution profile** of individual and grouped stages of a validated multistage impactor…*

APSD (*middle* flow rate)





Yu Liu, Heliyon 8 (2022) e10174

- The equivalence at all FR fulfilled (CI within 0.85-1.18), except mouthpiece, stage 7 and MOC
- These stages, in particular stage 7 and MOC are characterized by small deposition and high variability
- Deposition comparable on stages represented by particles of 1-6 µm (considered as clinically relevant)

Case study - in-vitro comparison (7)

*The comparison should be performed per impactor stage **or justified group of stages**…*

Group	Respective parts of human respiratory tract	T/R geometric mean ratio (middle flow rate)	CI lower	CI upper	Equivalence
Level 1	Oral cavity, Swallow fraction	1.106	1.097	1.113	YES
Level 2	Larynx, pharynx, primary bronchi	0.978	0.974	0.981	YES
Level 3	Bronchi, bronchioles	1.018	1.009	1.027	YES
Level 4	Alveoli	0.963	0.912	1.019	YES

- 4 groups were proposed representing major parts of human respiratory tract
- The equivalence at each group (at all flow rates) was demonstrated (CI within the 0.85-1.18)
- **No pre-specified protocol was available → Step 2 (PK) was initiated**

Updated Quality guideline (Rev 1) – major changes for DPIs

API	• Complete description of micronisation process with in-process controls
Pharmaceutical development	• 3 batches of DP with at least 10 inhalers/units from each batch • UDD and FPD over patient flow rate: FR 30-90 L/min or pressure drop 2-6 kPa • Re-priming tested on worst-case scenarios • Effect of environmental moisture: 25°C/70% RH or higher humidity specifically mentioned For capsule based DPIs lower humidity (e.g., 35% RH or 40% RH) to be tested • Simulation of dropping from EMA Q&A
Manufacture	• Conditioning time before batch release to be specified • For combination products yield of the final assembling step to be reported
Excipients	• Requirements for novel excipients defined
Specification - FPD	• Validated alternative to multistage impactor (AIM – abbreviated impactor method) • Specification range ±25% from EMA Q&A
Container Closure system	• Pictures to be provided • Reference to MDR • Reference to *Guideline on the quality requirements for drug device combination products*
Lifecycle management	• Examples of significant changes provided

Updated OIP guideline (Rev 2) – key updates for in-vitro comparisons

- **Stepwise approach** *officially* required
- The **core in-vitro criteria remain unchanged** with some overlapping requirements being removed
- **APSD requirements specified**:
  - **Grouping limited to stages with low deposition** (<5% of DD)
  - Non-sized fractions (e.g. IP/Presep) can be one group
  - **At least four groups with defined cut-off** (non-overlapping, NMT 3 stages in 1 group)
  - Similarity concluded if the 90% CI for the observed ratio of the geometric means of TEST and REF within the acceptance limit of ±15%, assuming log-normal distribution of data (85-118%)
  - **Not meeting the acceptance criteria at some stages/groups acceptable in exceptional cases**, but the number of samples should be sufficient to minimise the risk for Type II-error.
- **DPIs flow rate dependency** (FRD):
  - Resistance ±15% vs REF: comparison at 3 pressure drops (2-6 kPa) or 3 FR
  - Resistance >15% vs REF: comparison at 3 pressure drops (2-6 kPa)
  - **Two types of graphs required** for FPD vs pressure drops/FR
  - **If dependency of TEST > REF: additional PK data with trained healthy volunteers or patients**

Conclusions

Updated guidelines:

- Stepwise approach confirmed
- No revolutionary changes for DPIs – however each case requires separate evaluation
- DPIs previously developed by Polpharma meet the latest requirements

Case study:

- Extensive development carried out with QTPP and CQA defined
- All studies performed acc. to the Quality guideline and OIP guideline
- Multiple REF batches tested and representative batches selected for in-vitro studies
- APSD comparable on group of stages but not on every single stage
- At the end of step 1 the Applicant concluded that TE needs to be supported by PK studies (step 2)
- **PK studies confirmed BE!**

→ Define your TE acceptance criteria in advance (pre-specified protocol) and stick to them!

Thank You!