CBG MEB
MEDICINES EVALUATION BOARD

Orally Inhaled Products – Guideline Update

Carolien Versantvoort

Senior clinical pharmacology assessor

GOOD MEDICINES USED BETTER

Disclaimer

I attend this conference as an individual expert. The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the Medicines Evaluation Board or or any of the working parties of the European Medicines Agency or reflecting the position of the Medicines Evaluation Board or EMA.

EMA Guidance on 'generic' applications for orally inhaled products

1996

Note for guidance on the clinical requirements for *locally applied, locally acting* products containing known constituents. CPMP/EWP/239/95 final

2004 - 2010

Guideline on the requirements for clinical documentation for Orally Inhaled Products including the requirements for demonstration of *therapeutic equivalence between two inhaled products* for use in treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents. CPMP/EWP/4151/00 Rev. 1

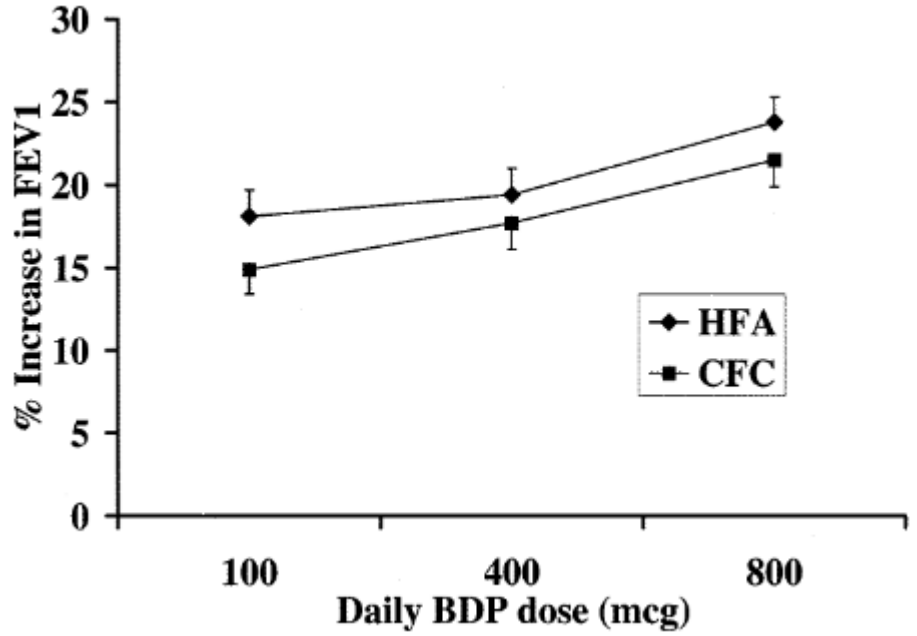
2024

Draft guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD) EMA/CHMP/101453/2024
Consultation dates: 12/04/2024 to 30/10/2024

OIP guideline 2010 ‘generic’ medicines

Corner stones of OIP guideline

- Therapeutic equivalence
  - In vitro equivalence
  - Pharmacokinetic equivalence in patients
  - Pharmacodynamic equivalence
  - Clinical equivalence
- Therapeutic equivalence should be demonstrated in all populations



Stepwise approach not required !!

OIP guideline 2010 ‘generic’ medicines
In vitro equivalence

- The product contains the same active substance (i.e. same salt, ester, hydrate or solvate, etc.).
- The pharmaceutical dosage form is identical (e.g. pMDI, non-pressurised MDI, DPI, etc.).
- The active substance is in the solid state (powder, suspension)
- Any qualitative and/or quantitative differences in excipients should not influence the performance of the product
- Any qualitative and/or quantitative differences in excipients should not change the safety profile of the product.
- The inhaled volume through the device to enable a sufficient amount of active substance into the lungs should be similar (within +/- 15%).
- 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.
- The inhalation device has the same resistance to airflow (within +/- 15%).
- The target delivered dose should be similar (within +/- 15%).

Labelling at that time was not based on delivered dose!

OIP guideline 2010 'generic' medicines
In vitro comparison: particle size distribution profile

- A validated multistage impactor method (Anderson cascade, Next generation)
- At least 4 groups of stages relevant for efficacy and safety

Groups of ACI Stages	Log Means		T/R Ratio	90% CI for T/R Ratio			
	Test group	Ref. group		Lower Limit (%)	Upper Limit (%)	In limits of ? 0.85-1.18	0.80-1.25
IP	11.6924	9.43782	1.23889	120.540	127.331	NO	NO
S0	0.1779	0.46126	0.38570	33.536	44.359	NO	NO
S1	0.1656	0.40292	0.41096	37.132	45.484	NO	NO
S2	0.4878	0.69914	0.69777	62.984	77.304	NO	NO
S3	2.3687	2.51234	0.94282	88.433	100.519	YES	YES
S4	4.0385	3.65255	1.10566	106.195	115.116	YES	YES
S5	2.3661	1.92485	1.22924	116.142	130.103	NO	NO
S3 to S5	8.7785	8.12420	1.08053	104.717	111.496	YES	YES
S6	0.3428	0.22168	1.54621	143.674	166.403	NO	NO
S7	0.1541	0.04858	3.17199	278.204	361.659	NO	NO
S6 + S7	0.4970	0.24557	2.02389	186.321	219.844	NO	NO
FPM	9.7330	8.61791	1.12939	109.393	116.600	YES	YES

OIP guideline 2010 ‘generic’ medicines
In vitro comparison: particle size distribution profile

- A validated multistage impactor method (Anderson cascade, Next generation)
- At least 4 groups of stages relevant for efficacy and safety
- With and without spacing device
- A range of flow rate (spanning 10-90 percentile of patients flow rate range)
- At least 3 batches test and reference product
- The maximum allowable in vitro difference should be indicated and justified pre-specified, e.g. +/- 15% may be justifiable, 90% CI should be calculated.

If the product does NOT satisfy ALL of these pharmaceutical criteria

for equivalence, in vivo studies should be performed.

OIP guideline 2010 ‘generic’ medicines
Pharmacokinetic equivalence

- PK study in patients – but which patients?
- Equivalence for efficacy: pharmacokinetic study with charcoal
- Equivalence for safety: pharmacokinetic study without charcoal
- pMDI: PK study with and without spacing device

Patient population

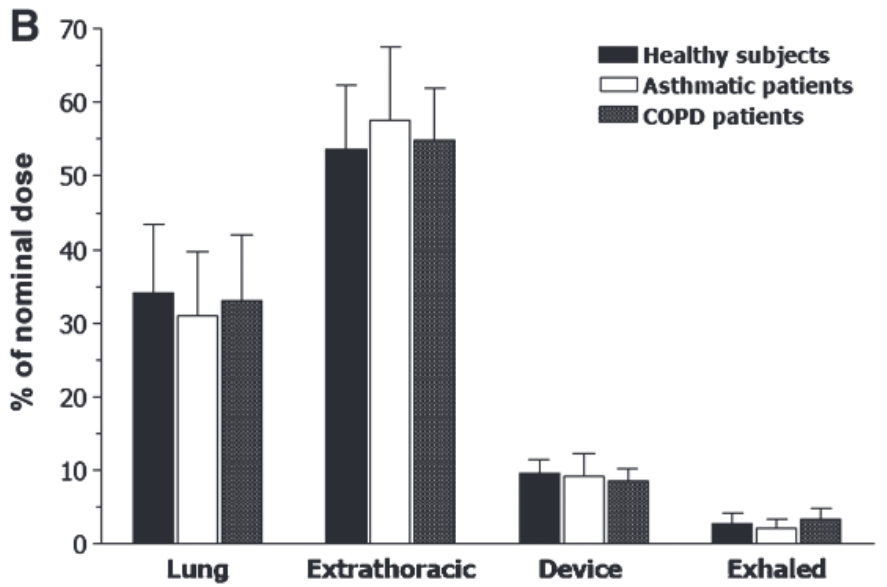
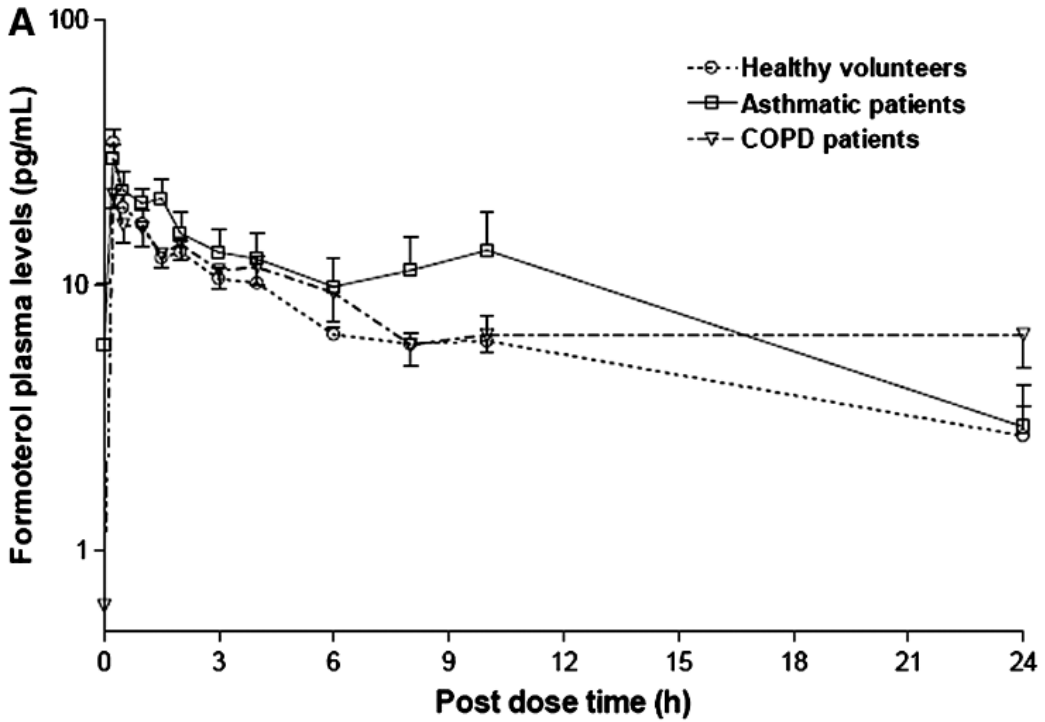


FIG. 2. (A) Scintigraphy in individual subject and (B) histogram showing mean (+standard deviation) drug deposition in



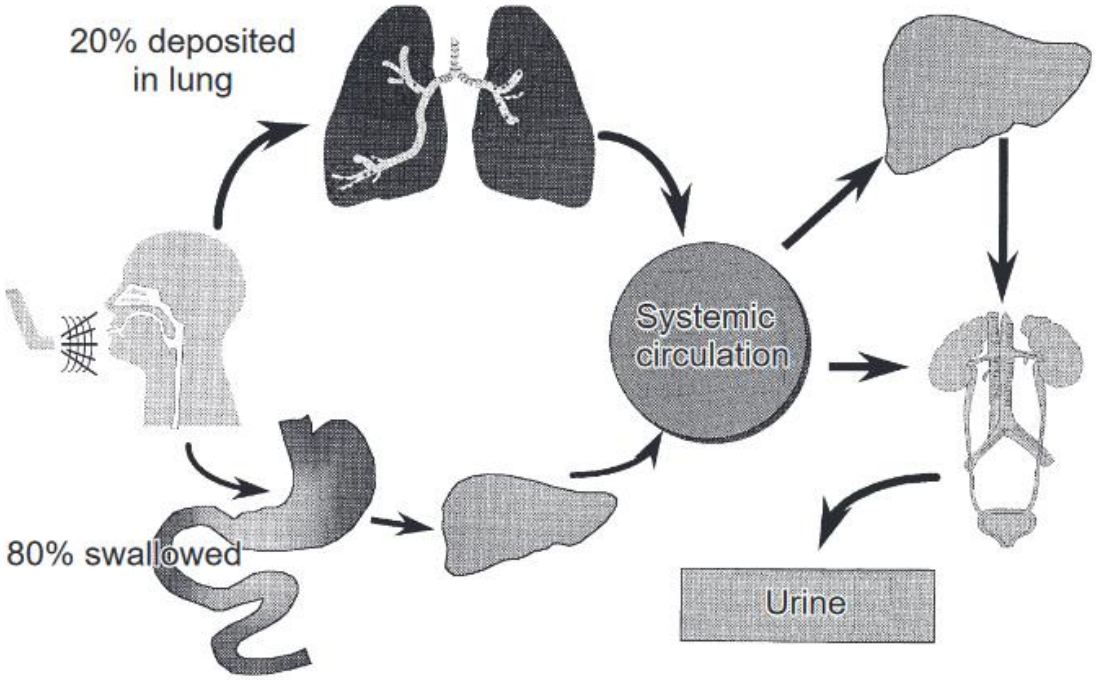
De Backer et al, 2010 J. Aerosol Med. Pulm. Drug Del.

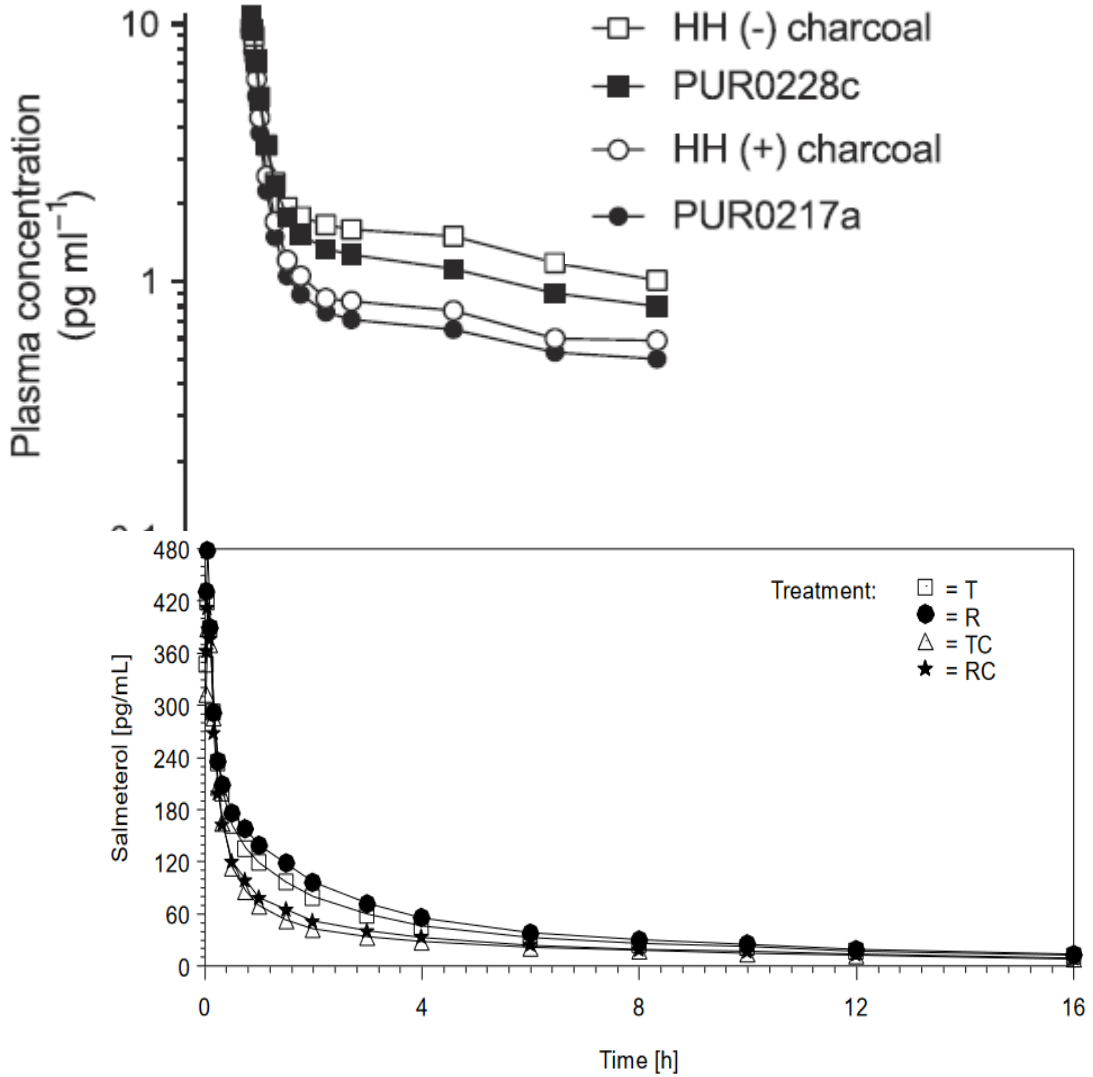
PK studies in healthy subjects – extrapolation by means of comparable flow dependency

OIP guideline 2010 ‘generic’ medicines
Pharmacokinetic equivalence

- PK study in patients – but which patients? → healthy subjects
- Equivalence for efficacy: pharmacokinetic study with charcoal
- Equivalence for safety: pharmacokinetic study without charcoal
- pMDI: PK study with and without spacing device

OIP guideline 2010 ‘generic’ medicines
Pharmacokinetic equivalence:
efficacy (with charcoal) and safety (without charcoal)





OIP guideline 2010 ‘generic’ medicines
Pharmacokinetic equivalence

- PK study in patients – but which patients? → healthy subjects
- Equivalence for efficacy: pharmacokinetic study with charcoal
- Equivalence for safety: pharmacokinetic study without charcoal
- pMDI: PK study with and without spacing device

pMDI: PK study with and without spacing device

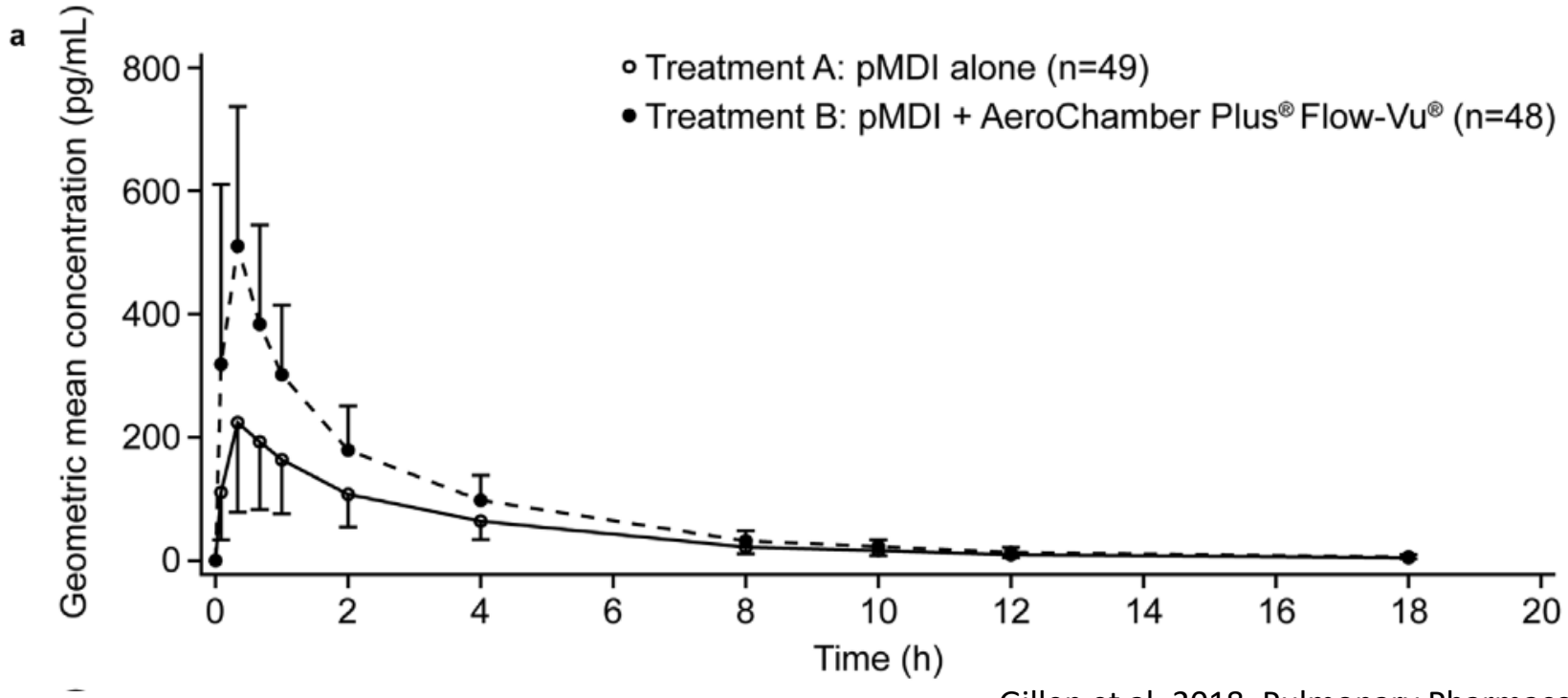
Spacers are advised for patients who have difficulty coordinating inhalation and handling the device i.e. paediatric asthma patients and…..?

Frequency of Correct, Acceptable, and Poor Inhalation Techniques and Their Changes Over Time

Period	Device	Correct	Acceptable	Poor
1975-2014	All	31 (28-35)	41 (36-47)	31 (27-36)
1975-1995	All	33 (26-40)	35 (26-45)	32 (26-37)
1996-2014	All	31 (26-36)	44 (39-59)	31 (25-37)
1975-2014	MDI	…	37 (32-42)	38 (30-46)
1975-2014	DPI	…	44 (34-54)	23 (18-29)

Sanchis et al, Chest 2016

PK study with an without spacer



Gillen et al.,2018, Pulmonary Pharmacol Ther

PKWP evaluation early 'generic' applications <2013 discussion points within EU

Requirements of PK bioequivalence studies for orally ingested and orally inhaled products.

	orally ingested immediate release products	orally inhaled pMDI and DPI products
Potency of batch used in PK study, which parameter? Quality control of batch?	• active substance ± 5% of specification • dissolution test criteria (e.g., F2 factor)	• mean delivered dose ±10-15% of target • fine particle dose – no criteria set (innovator products FPD is highly variable)
criteria for batch selection	• test content should not differ by more than 5% from reference	• no criteria set
acceptance limits - widening allowed based on intrasubject variability	• 90% CI within 80-125% • Yes	• 90% CI within 80-125% • Yes
waiver for other strengths	• composition dose proportional • dissolution test criteria	• composition dose proportional • dose linearity of FPD/APSD (no criteria set)
waiver of PK study	• BCS classification	• Waiver of lung deposition of safety study possible when oral bioavailability is negligible
PK study in patients In healthy subjects - extrapolation	• Only in case of toxicity	• Which patients (mild-severe) • Flow rate dependency (no criteria set)

Quality specific type of product guidance

Specific types of product - Orally inhaled products

1. What is considered as an acceptable range of fine particle dose (FPD) in the finished product specification?
2. The batches of the test and the comparator chosen for the PK study need to be representative. What is considered as a representative batch?
3. How to demonstrate dose proportionality in vitro for waiving of PK studies?
4. How to study flow-rate dependency in vitro for waiving PK data in patients?

https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-guidelines/quality-medicines-qa-introduction/quality-medicines-questions-answers-part-2

Clinical Pharmacology and phamracokinetic questions and answers

3.3 Regarding the evaluation of orally inhaled medicinal products, to what extent do plasma levels reflect bio-availability in the lung? January 2015

3.4 Evaluation of orally inhaled medicinal products: can I scale acceptance limits (for Cmax and perhaps AUC) to allow for variability in reference product for fine particle dose? January 2015

4.11 What is the recommendation on the most sensitive analyte and the required studies for establishing therapeutic equivalence by means of pharmacokinetic data for orally inhaled products containing beclomethasone dipropionate? New March 2020

https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/clinical-pharmacology-pharmacokinetics-questions-answers

Draft OIP 2024

1 16 March 2024
2 May 2018 (Version 4.0)
3 EMA/CHMP/101453/2024
4 Committee for Medicinal Products for Human Use (CHMP)

5 Guideline on the requirements for demonstrating
6 therapeutic equivalence between orally inhaled products
7 (OIP) for asthma and chronic obstructive pulmonary
8 disease (COPD)
9

Draft OIP guideline

Executive summary

This guideline is the 2nd revision of the CHMP Guideline formerly called "Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents". It addresses the requirements for demonstration of therapeutic equivalence (TE) between orally inhaled products containing the same active moiety(ies).

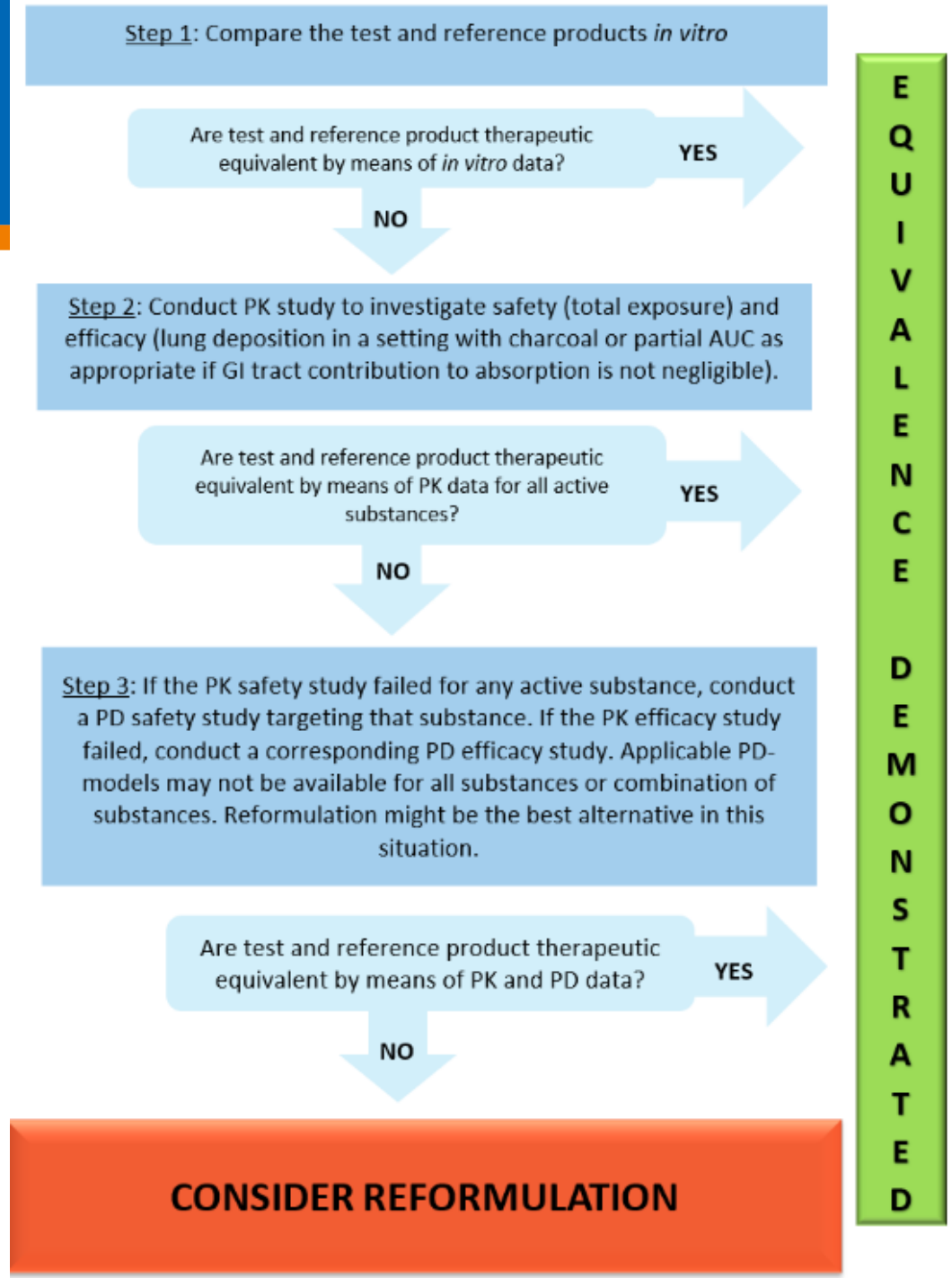
It is now clarified that the demonstration of TE between OIP is based on a stepwise approach, where TE could be demonstrated *in vitro* if all *in vitro* requirements are fulfilled or else preferably by means of pharmacokinetics if equivalent systemic exposure (as a surrogate marker for safety) and equivalent lung absorption/deposition (as a surrogate marker for efficacy) is demonstrated in spite of some *in vitro* differences. It is generally not recommended to aim at demonstrating TE using pharmacodynamic or clinical endpoints as these are deemed insensitive. The text on how to apply pharmacodynamic and clinical endpoints is thus considerably shortened or deleted.

The section on children and adolescents is shortened and it is now said to be acceptable to apply the same age limits as for the reference product in many cases. The conditions for extrapolation of PK data from healthy volunteers to the full patient population are also described.

In the previous guideline there was also some general information on pharmaceutical forms which is now deleted.

Draft OIP 2024
A step-wise approach (Chap 4)

- In vitro equivalence evaluation is **required** (Chap 5)
- Only the parts for which no in vitro equivalence is demonstrated, need further evaluation by PK studies (Chap 6)
- It is generally not recommended to aim at demonstrating TE using pharmacodynamic or clinical endpoints as these are deemed insensitive. (Chap 7)

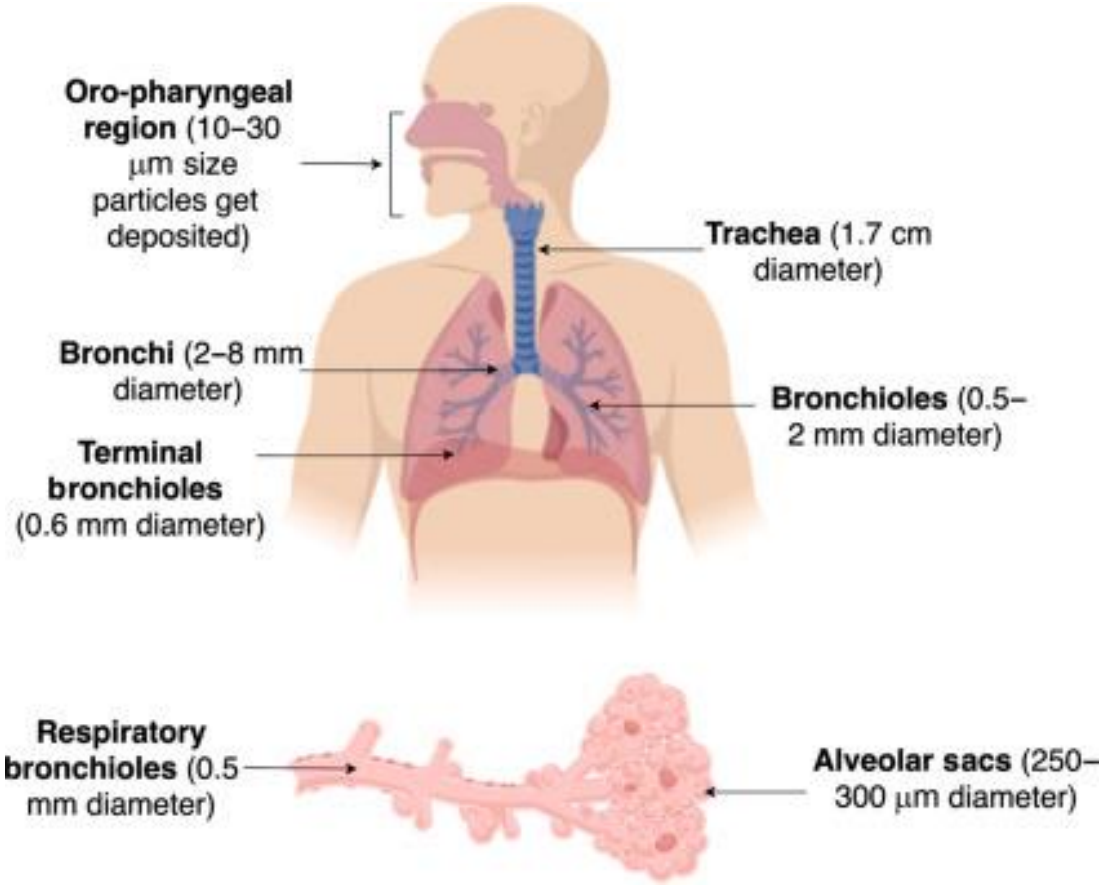


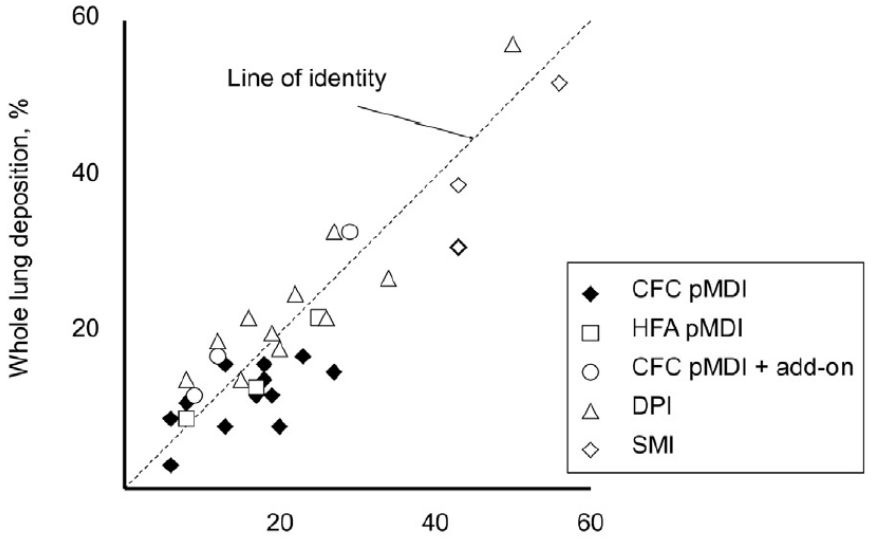
Chap 5.1
In vitro criteria for demonstrating therapeutic equivalence

Approximately the same in vitro parameters as in OIP 2010

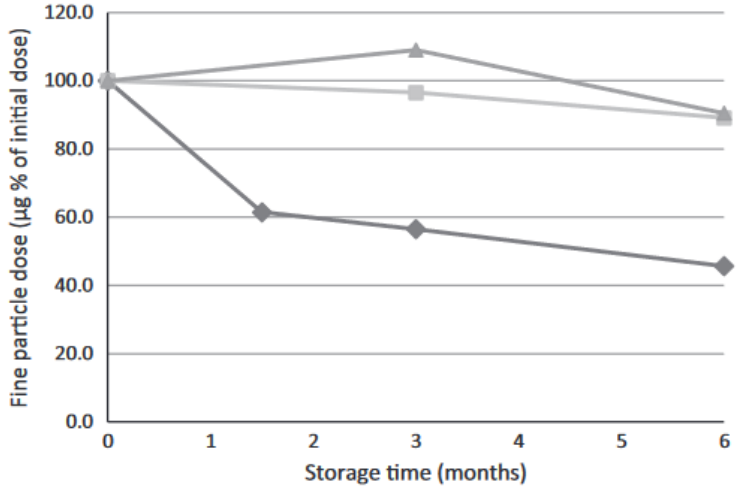
- More guidance on grouping
- More guidance on APSD evaluation and criteria: 90% CI is within the acceptance limit of ±15% (85.00-117.65%).
- More guidance of number of batches/samples

Batch selection – variability in FPD
Lung deposition and particle size

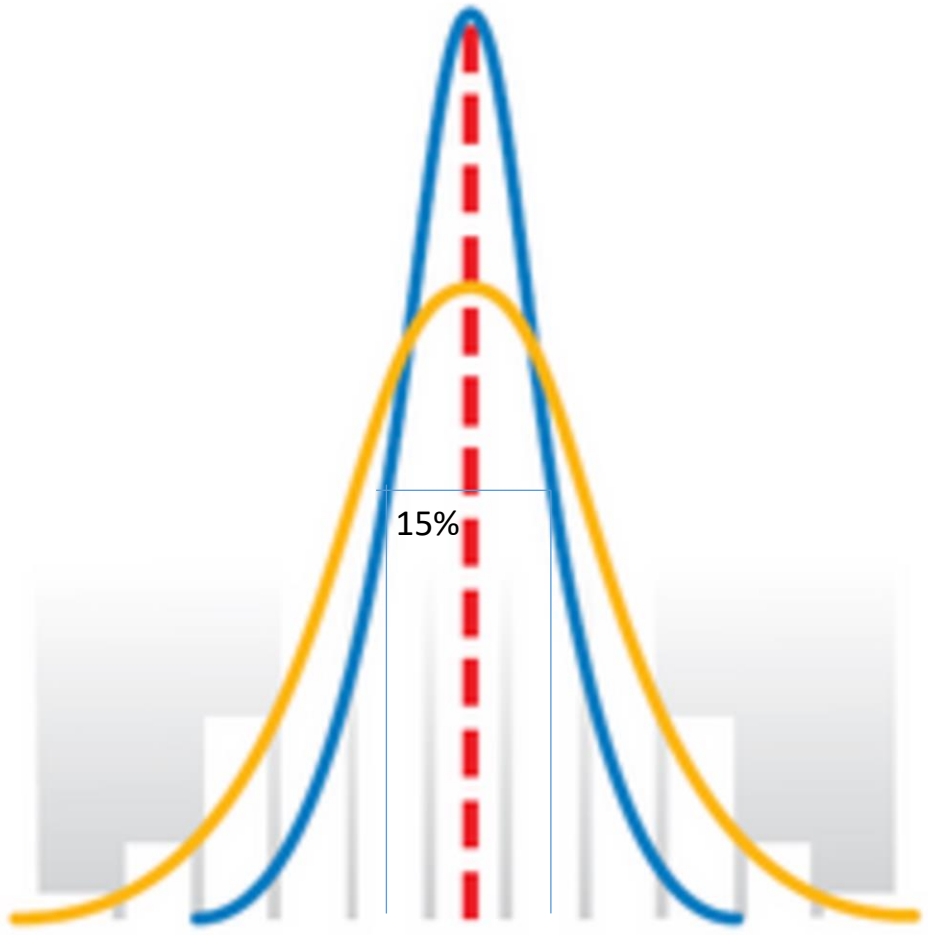




Newman et al. 2000 Int J Pharm

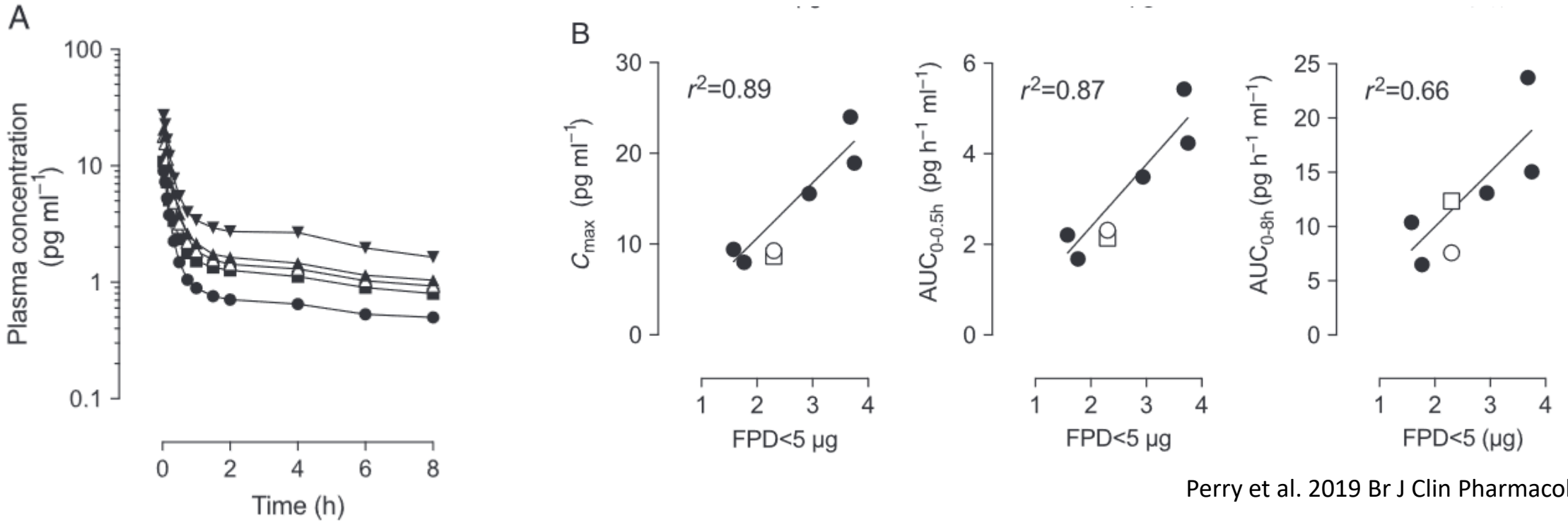


Batch selection – variability in FPD - FPD
Representative batch for PK study



At least 5 batches
Within 15% of median value observed
Values of test and reference batches in PK study as similar as possible
Chapter 5.2.3. & 6.3.2. Draft OIP guideline

Batch selection – variability in FPD
IVIVC example tiotropium batches with different particle distribution

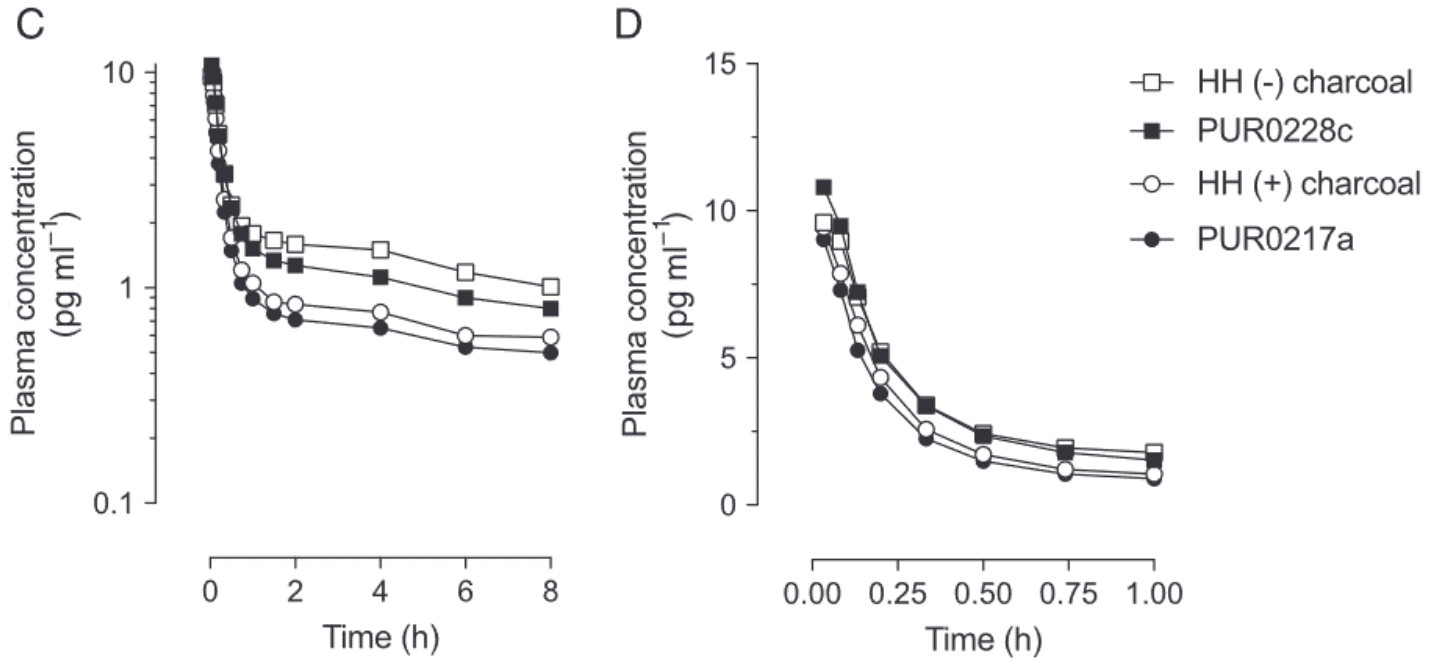


Perry et al. 2019 Br J Clin Pharmacol

Use of side batches
IVIVC
Fixed dose combinations select different batches

Chapter 6.3.2 and 6.4 Draft OIP guideline

PK Efficacy equivalence
(No) Charcoal and AUC0-30min



- Negligible contribution of intestinal absorption to exposure
- Very rapid lung absorption

Chapters 6.2.1 & 6.2.2
Draft OIP guideline

	C_{max} (pg ml^{-1})		$AUC_{0-0.5h}$ (pg h^{-1} ml^{-1})		AUC_{0-8h} (pg h^{-1} ml^{-1})	
	No charcoal	**Charcoal**	**No charcoal**	**Charcoal**	**No charcoal**	**Charcoal**
Geometric mean (%CV)	7.86 (74.1)	8.27 (65.6)	2.02 (56.2)	1.94 (42.6)	11.95 (28.7)	7.61 (24.1)
GMR and 90%CI	95.10 (83.02–108.95)		104.01 (94.48–113.90)		157.03 (144.85–170.23)	

Perry et al. 2019 Br J Clin Pharmacol

PK studies conducted in healthy subjects extrapolation to other populations

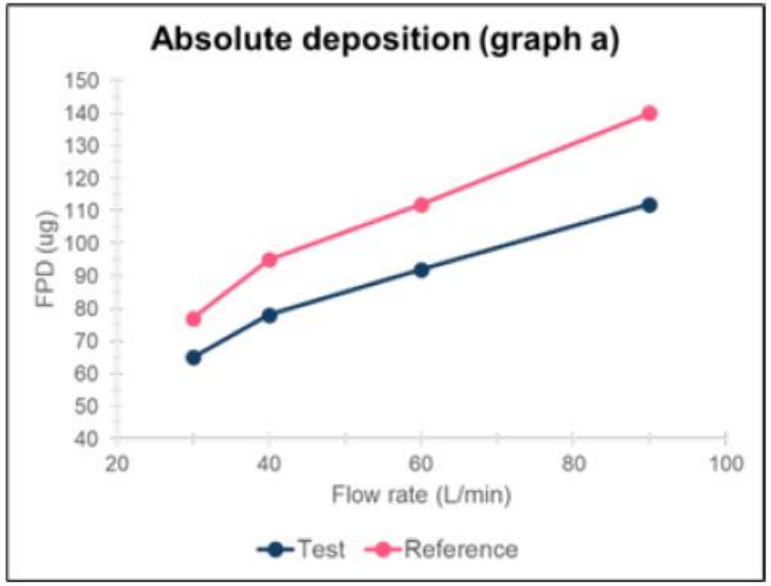
PK studies conducted in healthy subjects extrapolation to other populations

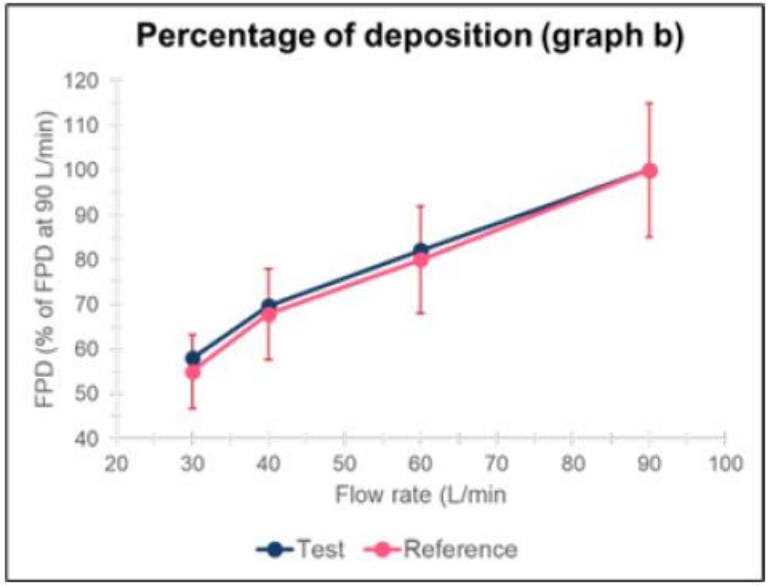
Inhaler type	Assessment priority	Minimal PIF literature (L/min)	Optimal PIF literature (L/min)	Cut-off value for suboptimal PIF	In-Check DIAL setting
Ellipta [5, 40]	1	30	60	60	Medium/low
Turbuhaler [5, 40]	2	30	60	60	Different for different molecules
Breezhaler [5, 40]	3	50	50	50	Low
Zonda[a]	4	20	39	30	High
Genuair [5, 40]	5	40	45	45	Medium
Novolizer [5, 40]	6	35	50	50	Medium
Spiromax [5, 40]	7	40	40	40	Medium
Diskus [5, 40]	8	30	60	60	Medium/low
HandiHaler [5, 40]	9	20	30	30	High
NEXThaler [5, 40]	10	35	35	35	Medium/high
Cyclohaler (Aerolizer) [5]	11	40	65	65	Low
Easyhaler [5, 40]	12	30	30	N/A	N/A
Forspiro [41]	13	30	60	60	Medium
Elpenhaler[b] [42]	14	30	60	60	Different for different molecules
Clickhaler [37, 43]	17	15	15	N/A	Medium

Flow rate dependency
Chap 5.2.1 draft OIP guideline

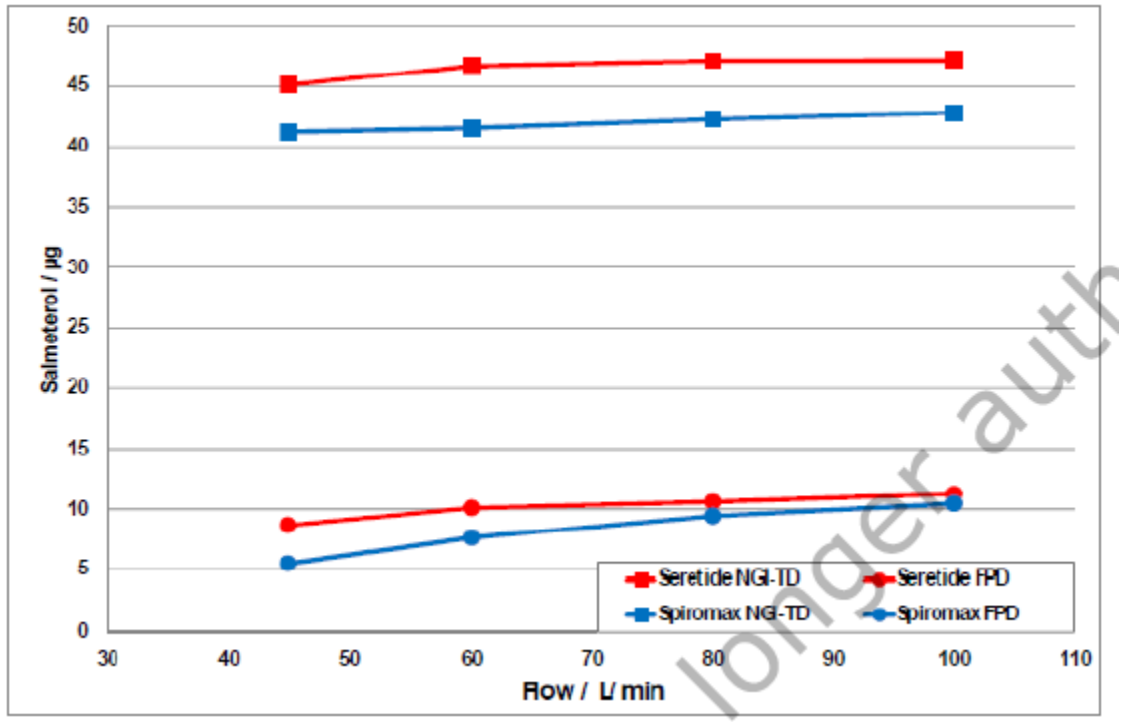
Flow rate dependency - extrapolation populations / strengths

Chap 5.2.1 provide guidance how to evaluate and report flow rate depenency





PK studies conducted in healthy subjects extrapolation to other populations



population	FS Spiromax	Seretide Accuhaler
paediatric asthma, age 4-11 years	85 (15)	86 (15)
adolescents asthma, age 12-17 years	107 (13)	109 (14)
adult asthma, age 18-45 years	108 (12)	111 (13)
COPD, age 55 years	88 (14)	91 (16)
healthy subjects, age 18-45 years	116 (12)	119 (11)

Chapter 8: Children and adolescents

Reference product has indication in children and adolescents

- In vitro equivalence demonstrated?
  - Device is known that it can be handled in children and adolescents → all population indications of the reference product are acceptable
  - Device not known that it can be handled → usability test in children and adolescents. If it can be handled correctly, all population indications of the reference product are acceptable
- In vitro equivalence not demonstrated but equivalence by PK studies in adults?
  - similar flow rate dependency of devices → adolscent population is acceptable
  - not similar flow rate dependency of devices – PK equivalence at a low inspiratory flow – adolescent population is acceptable

Chapter 9: usability study

- Medicinal product with an integral device need to be tested for usability in the intended population. ‘Guideline on quality documentation for 548 medicinal products when used with a medical device’ (EMA/CHMP/QWP/BWP/259165/2019), section 549 5.4.
- Moreover, a new integral medical device needs to be approved by Notified Body **before** application. (EU regulation 2017/745)
- Chap 9 provide guidance on the conduct and reporting of the usability study

Recap: differences between OIP 2010 and OIP 2024 'generic' applications

	OIP 2010	Draft OIP 2024
New products	X	
'Generic'	X	X
Therapeutic equivalence **Stepwise approach required** - In vitro comparison - Pharmacokinetic studies - Pharmacodynamic studies - Comparative clinical studies	 X X X X	 **X** X X X
Paediatric patients ➢ 12 years ➢ ≤ 12 years	TE for both efficacy and safety→ in vitro TE (usability study) or clinical TE	- TE for adults + similar flow dependency inhalers - In vitro TE (usability study)
Usability study		X

Nasal ‘generic’ products

Q&A 3.4 mentions that nasal generic products may follow principles of OIP guideline

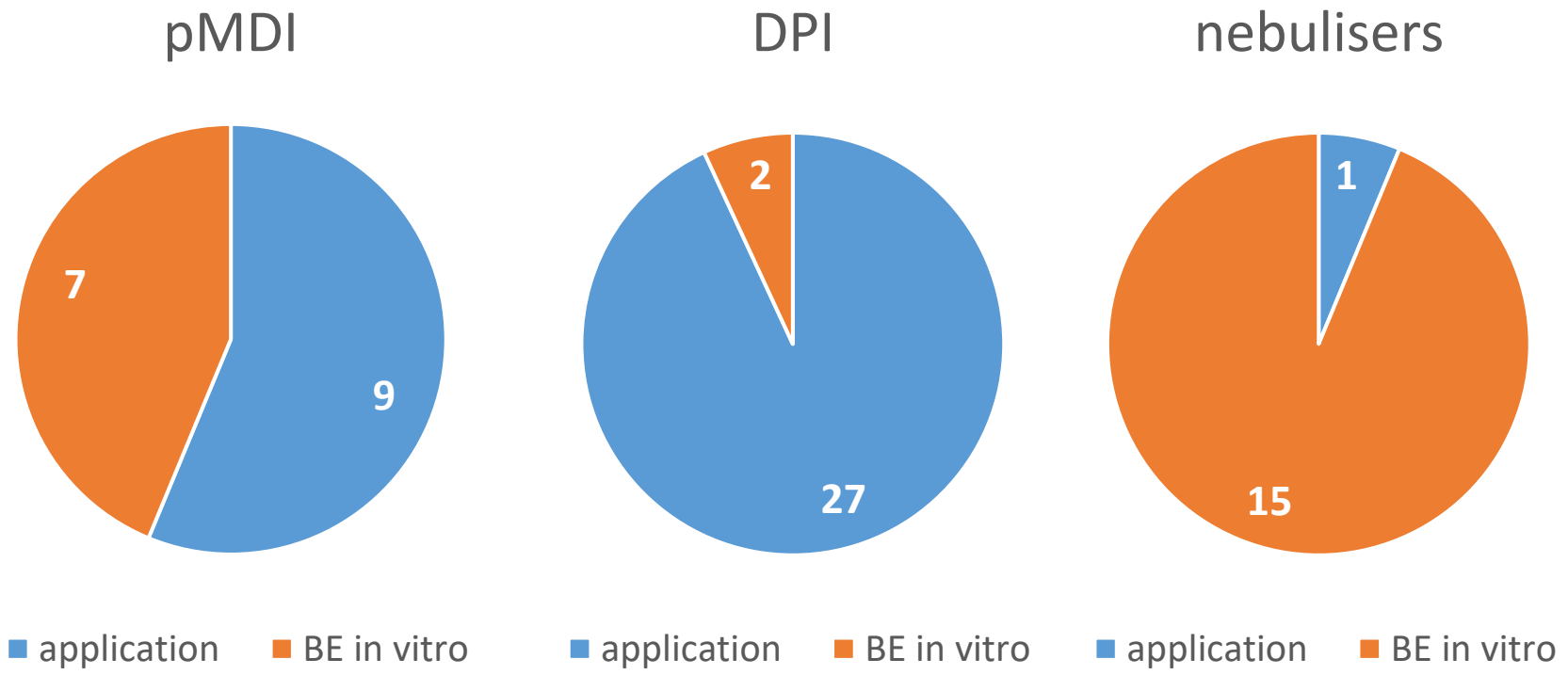
Concept paper for the development of a guideline on the demonstration of therapeutic equivalence for nasal products

Draft agreed by Methodology Working Party, Quality Working Party and Rheumatology and Immunology Working Party	May 2024
Adopted by CHMP for release for consultation	15 July 2024
Start of public consultation	25 July 2024
End of consultation (deadline for comments)	31 October 2024

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

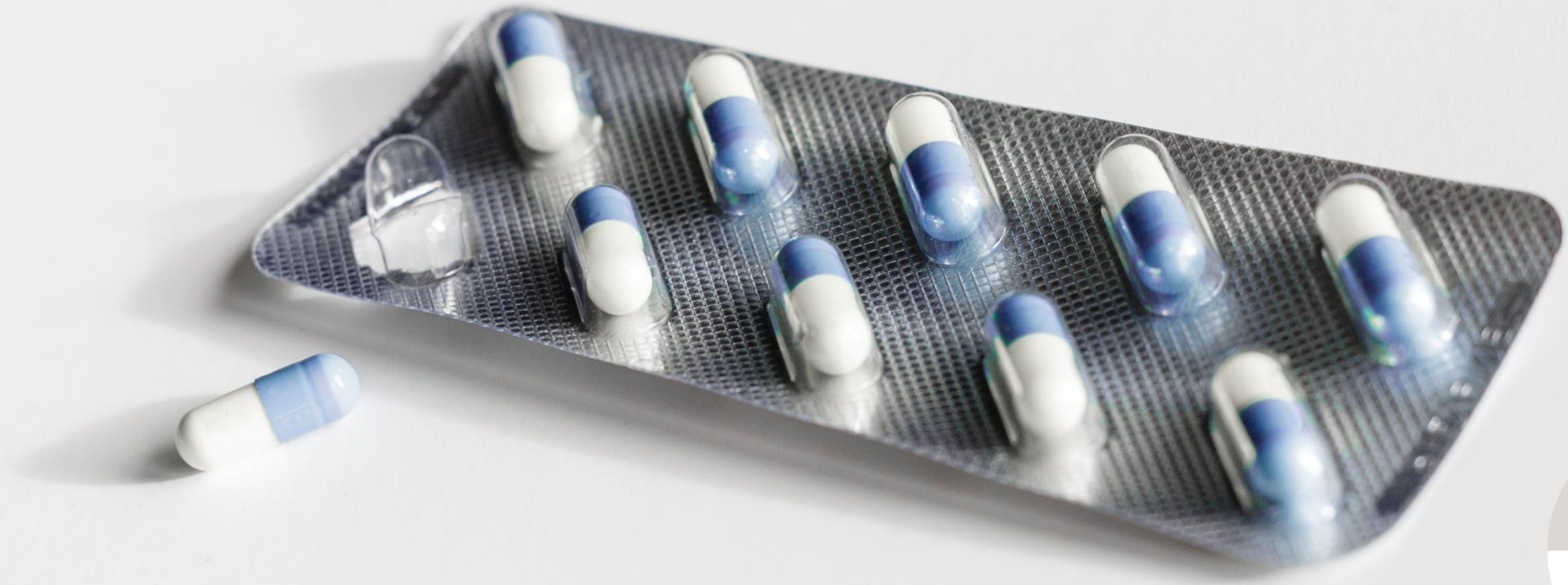
Keywords	Therapeutic Equivalence (TE), nasal

Experience as assessor 2012-2024
Therapeutic equivalence based on in vitro or PK equivalence



CBG MEB

MEDICINES EVALUATION BOARD



GOOD MEDICINES USED BETTER

Thank you