ORALLY INHALED PRODUCTS (OIP)

WHERE WE ARE AND WHERE WE GO

Vit Perlik

BioBridges 2024, September 26-27, Prague, CZ

OIP

The Scream
Author: Edvard Munch
Year: 1893

WHERE WE ARE: Regulatory Considerations

- **OIP guidance stepwise approach (CPMP/EWP/4151/00 Rev. 1, January 2009) + Q&A PKWP, Quality**

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 22 April 2004
CPMP/EWP/4151/00

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POINTS TO CONSIDER ON THE REQUIREMENTS FOR CLINICAL DOCUMENTATION FOR ORALLY INHALED PRODUCTS (OIP)

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 22 January 2009
Doc. Ref. CPMP/EWP/4151/00 Rev. 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2018
CPMP/EWP/239/95 Rev. 1, Corr.1*
Committee for Medicinal Products for Human Use (CHMP)

Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract[†]

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 18 October 2018
2 CHMP/QWP/708282/2018
3 Committee for Medicinal Products for Human Use (CHMP)

4 Draft guideline on quality and equivalence of topical
5 products

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

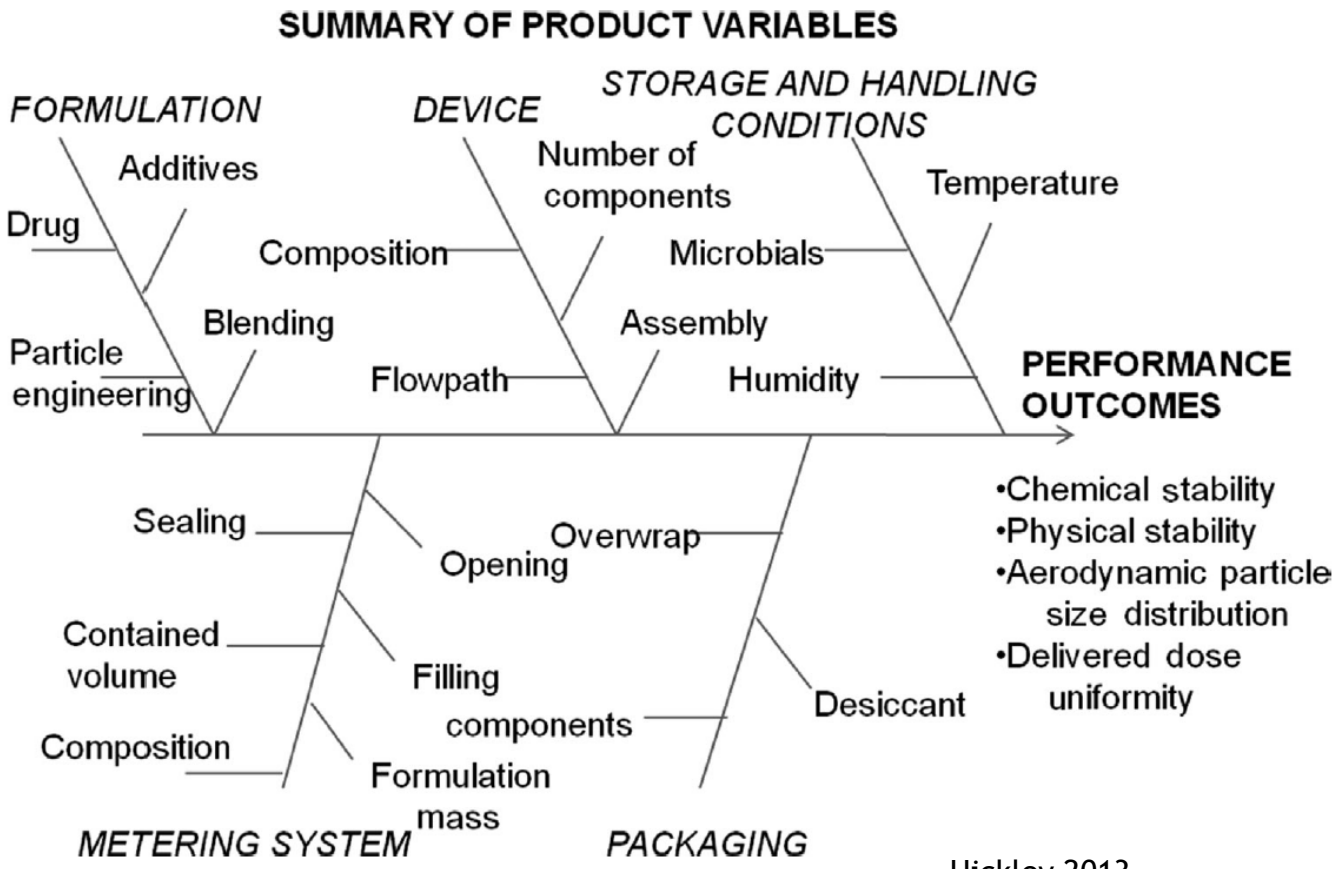
1 24 November 2023
2 EMA/CHMP/BMWP/35061/2024
3 Committee for Medicinal Products for Human Use (CHMP)

4 Concept paper for the development of a Reflection Paper
5 on a tailored clinical approach in Biosimilar development

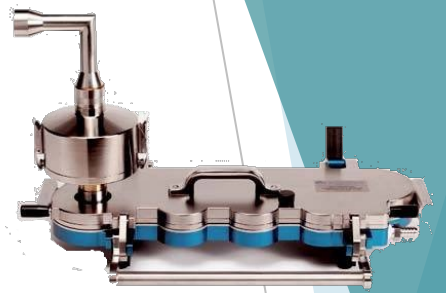
WHERE WE ARE: Regulatory Considerations

- **In vitro characterization**
- Pharmaceutical equivalence/evaluation
  - **Active substance in the same form** (i.e. salt, ester, hydrate etc.) and in the solid state (powder, suspension)
  - Identical pharmaceutical dosage form with **similar handling**
    - **Device: resistance to airflow, inhaled volume (within +/- 15%)**
    - Formulation/excipients: should not influence the product and its safety profile
    - **In vitro multistage impactor particle size characterization (within +/- 15%)**

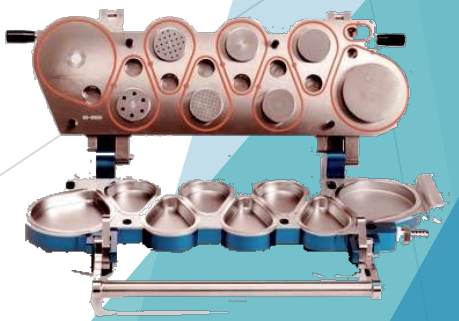
WHERE WE ARE: Development Considerations



Hickley 2013



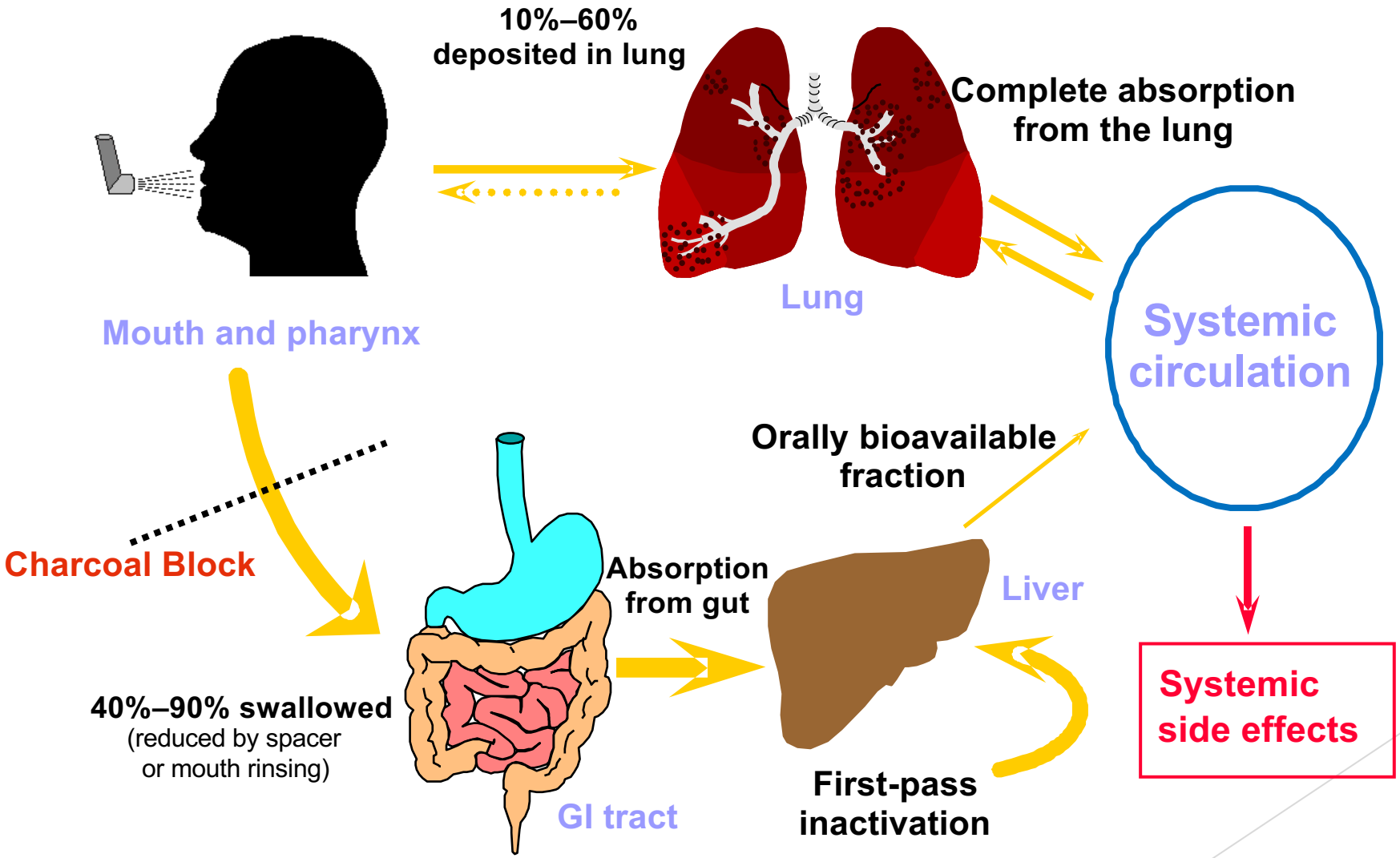
- **Aerosol characteristics**
  - **Size and shape of particles**
  - **Aerodynamic Particle Size Distribution (APSD)**
  - **Groupings**
  - **Resistance of the device**



Pharmacokinetic Equivalence/Evaluation

- **Pulmonary deposition - surrogate for efficacy**
  - **Describing extent (AUC) and rate (Cmax)** of absorption delivered via lungs **(charcoal block)**
  - Imaging studies possible however rather supportive
- **Systemic exposure - surrogate for safety**
  - Describing extent (AUC) and rate (Cmax) of absorption delivered via lungs and gastrointestinal tract
  - **Healthy volunteers vs Patients**
  - Methodology: CPMP/EWP/QWP/1401/98 Rev.1/ Corr Guideline on the Investigation of Bioequivalence
- **Therapeutic equivalence/evaluation (PD endpoints acceptable)**
- **Generally independent program for children is required considering the approved/target indications**

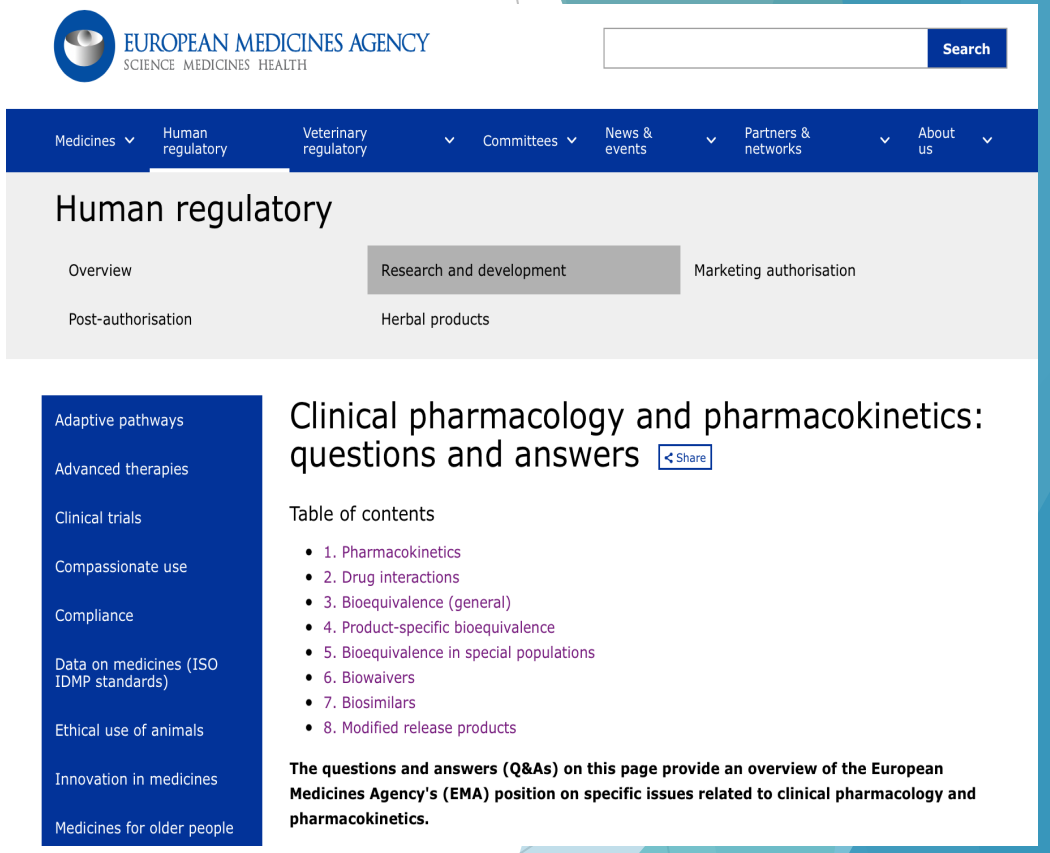
Pharmacokinetic Equivalence/Evaluation



EMA – Q&A OIP, pAUCs

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

- „In case the absorption of the drug in the lung is very quick (e.g., tmax ≤ 5 min) and absorption occurs before the contribution of gastrointestinal absorption is significant (e.g., salbutamol/albuterol, salmeterol), **AUC0-30 min might be acceptable as a surrogate for efficacy** and AUC0-t for safety. Thus, in this case, one study without active charcoal blockade is sufficient.“



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

EMA – Q&A OIP, IVIVC

- **Between- and intra-batch variability of the reference product**

The development of an IVIVC may be useful to correct the results of the PK study to justified parts of the APSD of the typical marketed batch of the reference product and the corresponding typical test product batch according to the proposed specifications. The IVIC could also be used as scientific support of the in vitro specification of the test product.

Q&A PKWP, EMA/618604/2008 Rev. 11, 2015

- **Valuable development tool**
- **Possible use of IVIVC for correction of the PK data**
- **Possible use of IVIVC to set the in vitro specification**

IVIVC: pAUC 0-20min ratios SUCCESS

Full dataset – Compound 1

X L/min				Y L/min			
Test/Reference				Test/Reference			
	R2_total		R2_P1-P2		R2_total		R2_P1-P2
FPD ≤3µm*/DD	0,7936	< 2,82 µm	0,9531	< 10,033 µm	0,8946	FPD ≤5µm*/DD	0,9561
FPD ≤5µm*/DD	0,7634	FPD ≤5µm*	0,9449	< 5,507 µm	0,8853	< 5,507 µm	0,8785
MOC	0,7374	Stage 5	0,9360	< 1,165 µm	0,8092	< 3,454 µm	0,8165
Throat	0,5807	FPD ≤3µm*	0,9284	<0,446 µm	0,7506	Stage 4	0,8049
Presep	0,5769	< 0,94 µm	0,9174	< 0,701 µm	0,7455	< 2,008 µm	0,7889
Stage 4	0,5150	< 1,66 µm	0,9161	FPD ≤3µm*/DD	0,7243	< 10,033 µm	0,7887
< 1,66 µm	0,4922	Stage 4	0,9129	Stage 6	0,7045	< 1,165 µm	0,7603
Stage 5	0,4797	FPD ≤3µm*/DD	0,9020	FPD ≤3µm*	0,6951	FPD ≤3µm*/DD	0,7530
FPD ≤3µm*	0,4795	FPD ≤5µm*/DD	0,8788	FPD ≤5µm*/DD	0,6835	Stage 3	0,6755
ED	0,4611	< 0,55 µm	0,8594	FPD ≤5µm*	0,6812	FPD ≤5µm*	0,6623

- Identified correlation parameters – ratios T/R for Y L/min
- < 5.507 µm
- < 10.033 µm

IVIVC: AUClast ratios SUCCESS

Full dataset

X L/min				Y L/min			
Test/Reference				Test/Reference			
	R2_total		R2_P1-P2		R2_total		R2_P1-P2
< 8,06 µm	0,94705	Stage 3	0,96068	Stage 3	0,58056	FPD ≤5µm*/DD	0,93875
< 4,46 µm	0,94033	FPD ≤5µm*	0,95271	< 5,507 µm	0,55373	< 5,507 µm	0,81719
FPD ≤5µm*	0,87533	< 4,46 µm	0,94056	< 10,033 µm	0,47576	Stage 3	0,80314
< 0,94 µm	0,82845	FPD ≤5µm*/DD	0,92308	Stage 7	0,41273	< 3,454 µm	0,66994
< 2,82 µm	0,81177	< 8,06 µm	0,92124	Stage 6	0,38131	Stage 7	0,63176
<0,34 µm	0,81014	< 2,82 µm	0,90747	< 3,454 µm	0,37819	Stage 4	0,63163
< 0,55 µm	0,79826	Stage 5	0,80387	< 1,165 µm	0,36048	< 0,701 µm	0,63086
Stage 5	0,79712	FPD ≤3µm*/DD	0,80297	< 0,701 µm	0,30204	< 2,008 µm	0,61986
Stage 6	0,77281	FPD ≤3µm*	0,80002	Stage 5	0,28877	<0,446 µm	0,61971
Stage 3	0,76705	< 0,94 µm	0,7763	< 2,008 µm	0,28847	Stage 6	0,61638

W/O Outliers

X L/min				Y L/min			
Test/Reference				Test/Reference			
	R2_total		R2_P1-P2		R2_total		R2_P1-P2
< 8,06 µm	0,97428	< 8,06 µm	0,99736	Stage 3	0,52713	Stage 1	0,81265
< 4,46 µm	0,9153	< 4,46 µm	0,97959	< 5,507 µm	0,41019	FPD ≤5µm*/DD	0,78694
<0,34 µm	0,75586	Stage 3	0,9465	< 10,033 µm	0,3641	Stage 3	0,78283
FPD ≤5µm*	0,70144	FPD ≤5µm*	0,82132	Stage 7	0,33562	Stage 7	0,66663
< 0,55 µm	0,68814	FPD ≤5µm*/DD	0,81875	Stage 6	0,2699	<0,446 µm	0,65063
Stage 3	0,65043	< 2,82 µm	0,73298	< 0,701 µm	0,2093	< 5,507 µm	0,6286
< 0,94 µm	0,64242	FPD ≤3µm*/DD	0,5914	< 1,165 µm	0,19927	MOC	0,61537
Stage 6	0,63807	Stage 5	0,57665	< 3,454 µm	0,18529	< 0,701 µm	0,58441
Stage 7	0,61234	FPD ≤3µm*	0,57397	Presep	0,14305	Stage 6	0,53879
< 2,82 µm	0,60673	< 0,94 µm	0,54416	Stage 5	0,13032	< 3,454 µm	0,43814

R2 total = all Pilots pooled
R2 P1-P2 = Pilot 1 and Pilot 2 (Pilot 3 excluded)

- IVIVC based on 2-3 studies, total program 6 studies
- Identified correlation parameters – ratios T/R for Y L/min
- Full dataset: < 8,06 µm; < 4,46 µm; FPD ≤5µm < 5.507 µm
- W/O Outliers: < 8,06 µm; < 4,46 µm

IVIVC: Absolute values SUCCESS

Compound 2 Cmax – Absolute values

Group (NGI)	IVIVC Slope	IVIVC Intercept	Reference in vitro pivotal data	Predicted in vivo pivotal Cmax	Observed in vivo pivotal Cmax	Difference Predicted / Observed
DD	11,98	393,88	127,13	1916,54	2149,43	-0,1084
FPD <5	24,14	274,24	133,42	3494,71	3356,11	0,0413

Group (NGI)	IVIVC Slope	IVIVC Intercept	Test in vitro pivotal data	Predicted in vivo pivotal Cmax	Observed in vivo pivotal Cmax	Difference Predicted / Observed
DD	13,83	-485,64	325,95	2018,79	1831,52	0,1023
FPD <5	30,31	-8,22	138,86	4200,52	4503,77	-0,0673

Compound 2 AUC – Absolute values

Group (NGI)	IVIVC Slope	IVIVC Intercept	Reference in vitro pivotal data	Predicted in vivo AUC	Observed in vivo AUC Mid	Difference Predicted / Observed
DD	27,51	579,22	127,13	4075,96	3883,86	0,0495
FPD <5	55,01	347,50	133,42	7687,09	6918,00	0,1112

Group (NGI)	IVIVC Slope	IVIVC Intercept	Test in vitro pivotal data	Predicted in vivo AUC	Observed in vivo AUC	Difference Predicted / Observed
DD	24,70	-534,43	325,95	3936,57	3471,74	0,1339
FPD <5	54,81	262,93	138,86	7873,91	7938,73	-0,0082

- IVIVC based on 3 studies, total program 5 studies
- DD and FPD identified to predict in vivo behavior

IVIVC: Absolute values SUCCESS

Compound 3 Cmax – Absolute values

Group (NGI)	IVIVC Slope	IVIVC Intercept	Reference in vitro pivotal data	Predicted in vivo pivotal Cmax	Observed in vivo pivotal Cmax	Difference Predicted / Observed
DD	7,65	3,35	3,42	29,50	26,20	0,1259
FPD <5	14,45	3,30	3,78	57,94	54,81	0,0571

Group (NGI)	IVIVC Slope	IVIVC Intercept	Test in vitro pivotal data	Predicted in vivo pivotal Cmax	Observed in vivo pivotal Cmax	Difference Predicted / Observed
DD	8,02	-13,40	9,61	24,61	28,28	-0,1297
FPD <5	14,85	0,20	4,04	60,24	61,12	-0,0143

Compound 3 AUC – Absolute values

Group (NGI)	IVIVC Slope	IVIVC Intercept	Reference in vitro pivotal data	Predicted in vivo pivotal AUC	Observed in vivo pivotal AUC	Difference Predicted / Observed
DD	28,25	-2,88	3,42	93,68	93,84	-0,0017
FPD <5	51,76	1,63	3,78	197,40	183,79	0,0740

Group (NGI)	IVIVC Slope	IVIVC Intercept	Test in vitro pivotal data	Predicted in vivo pivotal AUC	Observed in vivo pivotal AUC	Difference Predicted / Observed
DD	24,55	-41,28	9,61	75,06	99,37	-0,2446
FPD <5	45,30	0,73	4,04	183,90	189,09	-0,0274

- IVIVC based on 3 studies, total program 5 studies
- DD and FPD identified to predict in vivo behavior

WHERE ARE WE GOING?

OIP revision - IN VIVO part

End of consultation (deadline for comments)	30 October 2024

OIP revision – IN VIVO type of studies, pAUCs

EMA Q&A PKWP

- **3.3 Regarding the evaluation of orally inhaled medicinal products, to what extent do plasma levels reflect bio-availability in the lung?** January 2015
  - Non-charcoal
    - **Intestinal absorption to systemic exposure is negligible (5%)**
    - **t_{max} ≤ 5 min - partial AUC_{0-30}**
  - Charcoal
    - **Validated, literature OK**

OIP revision (draft)

6.2.1. Substances with negligible contribution from the gastrointestinal tract

For some orally inhaled medicinal products, the contribution from the GI tract to the total systemic exposure following inhalation is negligible (<5%) and a PK study without charcoal blockade can be used for both efficacy and safety comparisons. A low oral absolute bioavailability per se is, however, not synonymous with a negligible systemic contribution from GI absorption, since the contribution from the GI tract depends on the fraction of the dose being deposited in the lung and being swallowed, respectively, as well as on the fraction absorbed into the systemic circulation from each site. Reasons for the negligible contribution include poor intestinal absorption (e.g., chromoglycate, nedocromil), or an extensive first-pass metabolism (e.g., beclomethasone dipropionate, fluticasone, mometasone, ciclesonide).

6.2.2. Substances with significant contribution from the gastrointestinal tract

In this case there are two possible options as described below:

i. Study with activated charcoal

For drugs with significant oral bioavailability (e.g., budesonide, formoterol, salmeterol), a PK study with active charcoal can be performed to assess equivalence regarding efficacy. The charcoal blockade efficiency needs to be demonstrated (e.g., by using a method that has been shown to be effective in the literature).

ii. Early partial AUC in a study without activated charcoal

In the case that the absorption of the drug in the lung is very quick (e.g., median t_{max} ≤ 5 min) and absorption occurs before the contribution of GI absorption is significant (e.g., salbutamol/albuterol, salmeterol, glycopyrronium, formoterol), $AUC_{0-30\ min}$ is acceptable as a surrogate for efficacy and AUC_{0-t} for safety. Thus, in this case, a study without active charcoal blockade is sufficient.

OIP revision – IVIVC scaling

EMA Q&A PKWP

- **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?**
  - Safety - systemic exposure **90% CI ≤ 125.00**
  - Between- and intra- batch reference variability
    - Representative batches (±15% of reference median fine particle dose or APSD)
    - **IVIVC – T,R scaling or set the specification**
    - Testing of side batches – extremes

OIP revision (draft)

471 **6.4. In vitro in vivo correlation (IVIVC)**

472 As discussed in section 6.3.2 iv, the development of an IVIVC may be useful to correct the results of
473 the PK study to justified parts of the APSD of the typical marketed batch of the reference product and
474 the corresponding typical test product batch according to the proposed specifications in the rare
475 occasions when it is difficult to find representative batches. Adjustment or normalisation may be
476 acceptable if an IVIVC has been established previously between the *in vitro* parameters and the PK
477 parameters for systemic safety and lung deposition and has been pre-defined in the study protocol.
478 However, it should be noted that if a solid IVIVC was not established, normalisation will not be
479 acceptable. The correlation should be shown for all actives in a fixed-dose combination product since
480 the *in vivo* aerodynamic behaviour of the different drug particles may differ, although normalisation
481 may be performed for one substance alone if the two products are considered similar for the other
482 drug or no IVIVC is identified for that substance.

OIP revision - IVIVC comment

483 Due to inter-study differences, IVIVCs are expected to succeed only if they are investigated within a
484 single study. It is essential to point out that different products at the same strength and dose with a
485 different pattern of particle size distribution (PSD) should be included in the IVIVC.

- **Purpose of the IVIVCs is to establish and extrapolate the results to other studies**
- Most of the IVIVCs within OIPs based on the multiple studies (2-4; data on file…:-)
  - to cover mentioned areas of interest i.e. behavior of different batches of reference product
  - to target different formulations of test product
  - to investigate API PSD
  - to cover different strength of the product etc.

OIP revision PD – Out of the game

493 **7. Pharmacodynamic and clinical studies**

494 Endpoints as described in this guideline are deemed the most sensitive to detect differences between
495 test and reference products and thereby the most relevant to use when demonstrating TE. In the case
496 that data do not fulfil the acceptance criteria for PK endpoints, it is generally recommended to
497 reformulate the product. Only exceptionally TE will be deemed possible to be established without being
498 demonstrated kinetically, e.g., it could be applicable for some β_2-agonists.

499 If, however, other approaches with pharmacodynamic or clinical endpoints are considered, the study
500 designs must be such that assay sensitivity is clearly shown at an acceptable level. It is acknowledged
501 that for some active substances, and fixed combinations of such, appropriate study designs do not
502 exist, but a full clinical data package would need to be provided instead of taking the TE approach.

503 Appropriate endpoints for TE efficacy are measures of airway function and/or inflammation, and
504 appropriate endpoints for safety are measures of relevant biochemical and/or physiological
505 parameters. Safety assessments including monitoring of adverse events should always be included in
506 the efficacy studies regardless of design.

507 Regardless of the aim of the study, it is necessary to demonstrate that the sensitive part of the dose-
508 response curve for the PD parameter under investigation has been studied. To allow for estimation of
509 assay sensitivity, it is essential to include at least one non-zero dose level besides the level primary
510 investigated.

511 As for the PK studies (see section 6.3.2), the same batch of reference product should be used for
512 safety and efficacy PD studies, unless adequately justified, and should be representative for the

- **Reformulate or new development**
- Pharmacodynamic or clinical endpoints are deemed insensitive for therapeutic equivalence

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 October 2015
CHMP/EWP/2922/01 Rev.1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the clinical investigation of medicinal products for the treatment of asthma

Draft Agreed by Respiratory Drafting Group	**22 April 2013**
Draft Agreed by PDCO	15 March 2013
Adoption by CHMP for release for consultation	27 June 2013
Start of public consultation	1 July 2013
End of consultation (deadline for comments)	31December 2013
Agreed by Respiratory Drafting Group	May 2015
Adoption by CHMP	22 October 2015
Date for coming into effect	1 May 2016

This guideline replaces guideline CPMP/EWP/2922/01.

Keywords	*Asthma, medicinal products for the treatment of asthma, asthma in children, control of asthma, asthma severity*

OIP revision - IN VIVO – Other

- **8. Children and adolescents**
  - **Substantially simplified**
  - Handling (usability studies = human factor studies) and in vitro comparison highlighted

- **9. Usability studies**
  - **Reference to appropriate guideline added** ‘Guideline on quality documentation for medicinal products when used with a medical device’ (EMA/CHMP/QWP/BWP/259165/2019)
  - **Topic clarified**

OIP revision - Metabolites

EMA Q&A PKWP

- **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**

OIP revision (draft)

NA, part of product specific BE gdl?

- Beclomethasone dipropionate (BDP -parent) vs beclomethasone 17-monopropionate (B17MP - major metabolite)
  - **BDP - primary analyte for assessing lung deposition** (only non-charcoal study OK)
  - **B17MP – needed to support of systemic safety**
  - Sampling - within 1-2 mins after the end of the inhalation(s) and frequent in the first 10-15 mins

WHERE ARE WE GOING?

OIP revision - IN VITRO part

OIP revision - IN VITRO equivalence

- **5. *In vitro* comparison**
- **5.1. In vitro criteria for demonstrating TE**
  - More or less the same except of the APSD similarity demonstration
  - **Individual stages or groupings - OK**
  - 90% CI for the observed ratio of the **geometric test/reference means** within the acceptance limit of ±15% (85.00-117.65%)

    Alfredo Garcia-Arieta, 2014, DOI: 10.1089/jamp.2014.1130
  - **Mean of what???**

- „Other approaches of evaluation of similarity of the average APSD of the populations of test and reference products may be proposed…. These approaches should preferably be confirmed at preceding scientific advice."

Equivalence ?

- Investigation of **batch-to-batch PK variability** for Advair Diskus 100/50
- **One replication, plus three different batches of Advair Diskus 100/50 tested**
- **Estimation of ~40–70%** of residual error belong to batch-to-batch variability
- Number of subjects 29

Table 4 Bioequivalence assessment within and between manufacturing batches of Advair Diskus 100/50

	Geometric mean ratio (%)	
	Estimate	90% CI
Batch 1 (replicate A)– vs. –Batch 1 (replicate B)		
FP C_{max}	98.66	87.29–111.50
FP $AUC_{(0-t)}$	100.36	92.29–109.14
FP $AUC_{(0\text{-}tcommon)}$	100.68	92.87–109.15
FP $AUC_{(0-inf)}$	109.17	95.59–124.68
S C_{max}	95.15	82.75–109.42
S $AUC_{(0-t)}$	93.54	86.81–100.79
S $AUC_{(0\text{-}tcommon)}$	95.40	89.66–101.49
S $AUC_{(0-inf)}$	88.78	81.07–97.21
Batch 1– vs. –Batch 2		
FP C_{max}	65.05	58.56–72.26
FP $AUC_{(0-t)}$	77.02	71.67–82.77
FP $AUC_{(0\text{-}tcommon)}$	77.99	72.80–83.54
FP $AUC_{(0-inf)}$	78.39	69.66–88.21
S C_{max}	63.44	56.27–71.52
S $AUC_{(0-t)}$	76.73	71.97–81.81
S $AUC_{(0\text{-}tcommon)}$	79.64	75.55–83.95
S $AUC_{(0-inf)}$	80.72	74.68–87.25
Batch 1– vs. –Batch 3		
FP C_{max}	76.47	68.84–84.94
FP $AUC_{(0-t)}$	80.68	75.08–86.70
FP $AUC_{(0\text{-}tcommon)}$	81.37	76.06–87.06
FP $AUC_{(0-inf)}$	85.25	76.90–94.51
S C_{max}	80.24	71.17–90.46
S $AUC_{(0-t)}$	81.20	76.15–86.57
S $AUC_{(0\text{-}tcommon)}$	81.68	77.41–86.18
S $AUC_{(0-inf)}$	85.58	78.42–93.40
Batch 2– vs. –Batch 3		
FP C_{max}	117.55	104.16–132.65
FP $AUC_{(0-t)}$	104.75	96.43–113.79
FP $AUC_{(0\text{-}tcommon)}$	104.34	96.55–112.76
FP $AUC_{(0-inf)}$	108.75	95.63–123.68
S C_{max}	126.48	110.18–145.19
S $AUC_{(0-t)}$	105.82	98.30–113.91
S $AUC_{(0\text{-}tcommon)}$	102.56	96.48–109.02
S $AUC_{(0-inf)}$	106.02	96.04–117.04

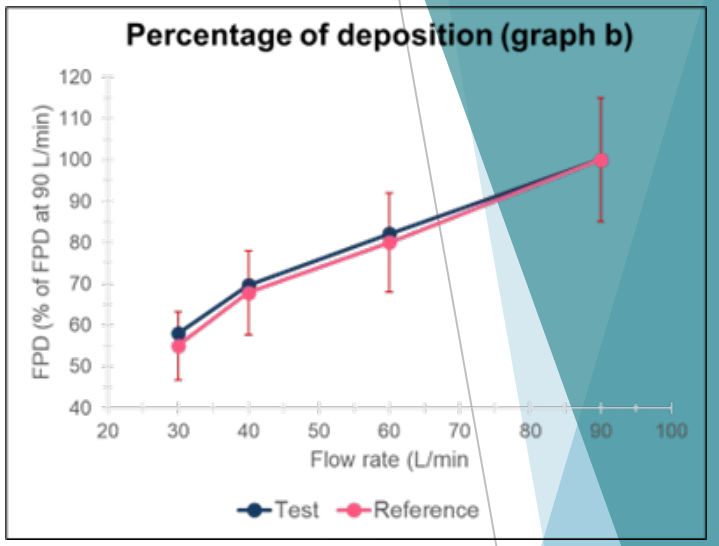
Burmeister Getz E, Carroll KJ, Jones B, Benet LZ. Batch-to-batch pharmacokinetic variability confounds current bioequivalence regulations: A dry powder inhaler randomized clinical trial. Clin Pharmacol Ther. 2016 Sep;100(3):223-31.

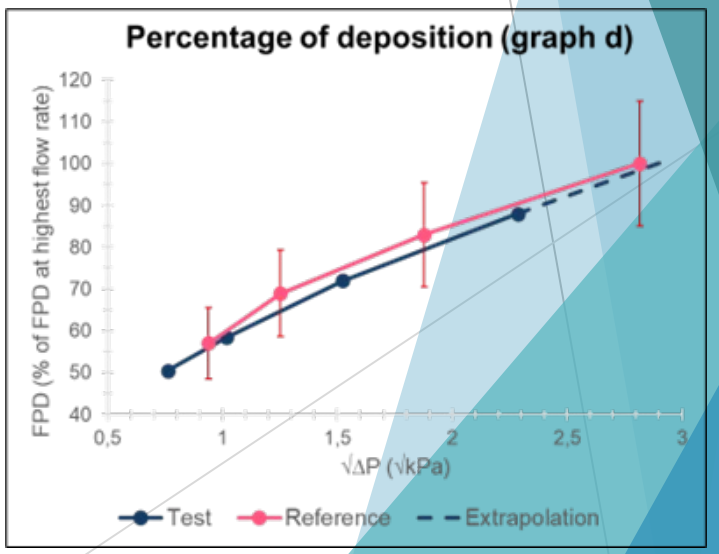
OIP revision - IN VITRO equivalence

- **5. *In vitro* comparison**
- **5.1. In vitro criteria for demonstrating TE**
  - **Mean of what???** for 90% CI ±15% (85.00-117.65%)
  - What is not reflected:
    - Inherent **variability of the APSD** (stages with small quantities, operator bias, humidity bias, electrostatic bias…)
    - **Clear impact on BE (**Burmeister Getz 2016**)**
    - **Batch-to-batch variability within- and between- is the reason to allow IVIVC based BE correction**
  - Other approaches of evaluation of similarity of the average APSD possible – subject to SA
  - **Proposal: Reference in vitro scaling…☺ = individualized approach to measurements and reference products**

OIP revision – IN VITRO flow rate

- **5.2.1. Flow rate dependency of dry powder inhalers**
  - **Topic substantially clarified** from Q&A Quality
  - Important for PK **extrapolation from healthy to patients**
  - Minimum of **four different flow rates over the range of 30 to 90 L/min**
    - no flow rate dependency or similar flow rate dependency
  - **Percentage of deposition (FPD – fine particle dose)** with 100% at the flow rate of 90 L/min
  - Similarity - point estimate test FPD within **± 15% of reference**





OIP revision - IN VITRO multiple strength

OIP revision (draft)

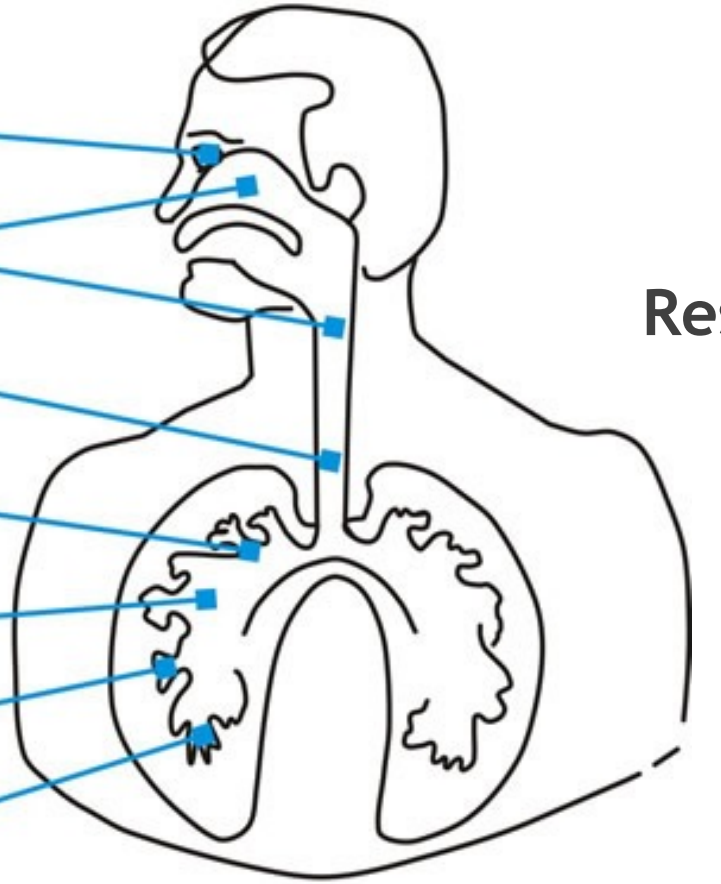
- **5.2.2. Investigation of several product strengths**
  - **Extrapolation possible** - comparable dose proportionality with test and reference product each
    - Proportionality for whole **APSD or group of stages**
    - ±15% acceptance range in each stage
    - DPI at three different flow rates (30 – 90 L/min)
    - **If not TE in vitro – bracketing** approach (testing the extremes)

EMA Q&A PKWP

3. How to demonstrate dose proportionality in vitro for waiving of PK studies?

PARTICLE SIZE DISTRIBUTION

Particle size	Fate
9 - 30 µm	visual pollution
5.5 - 9 µm	settle in nose/throat
3.3 - 5.5 µm	lodge in main breathing passages
2 - 3.3 µm	lodge in small breathing passages
1 - 2 µm	lodge in bronchi
0.3 - 1 µm	penetrate to bronchioles and alveoli
0.1 - 0.3 µm	penetrate to bronchioles and alveoli



Respirable fraction

- **Particles below 5µm**
- **Fine particles below 1µm largely exhaled**

Moore, Robson & Trinci (2011)

OIP revision - IN VITRO representative batch

OIP revision (draft)

- **5.2.3. Representative batches**
  - „**Variability in APSD between batches** of the reference product **or within** a single batch of a reference product through their storage period can be significant.“
    - **OK – … and how about the in vitro TE and its limits? …☺**
  - Commercial batches from market, different ages or shelf-life
  - **Minimum of 5 batches** (some companies used around 100)
  - Batch for *in vivo* study(-ies) close to the median „±15% is reasonable“

EMA Q&A PKWP

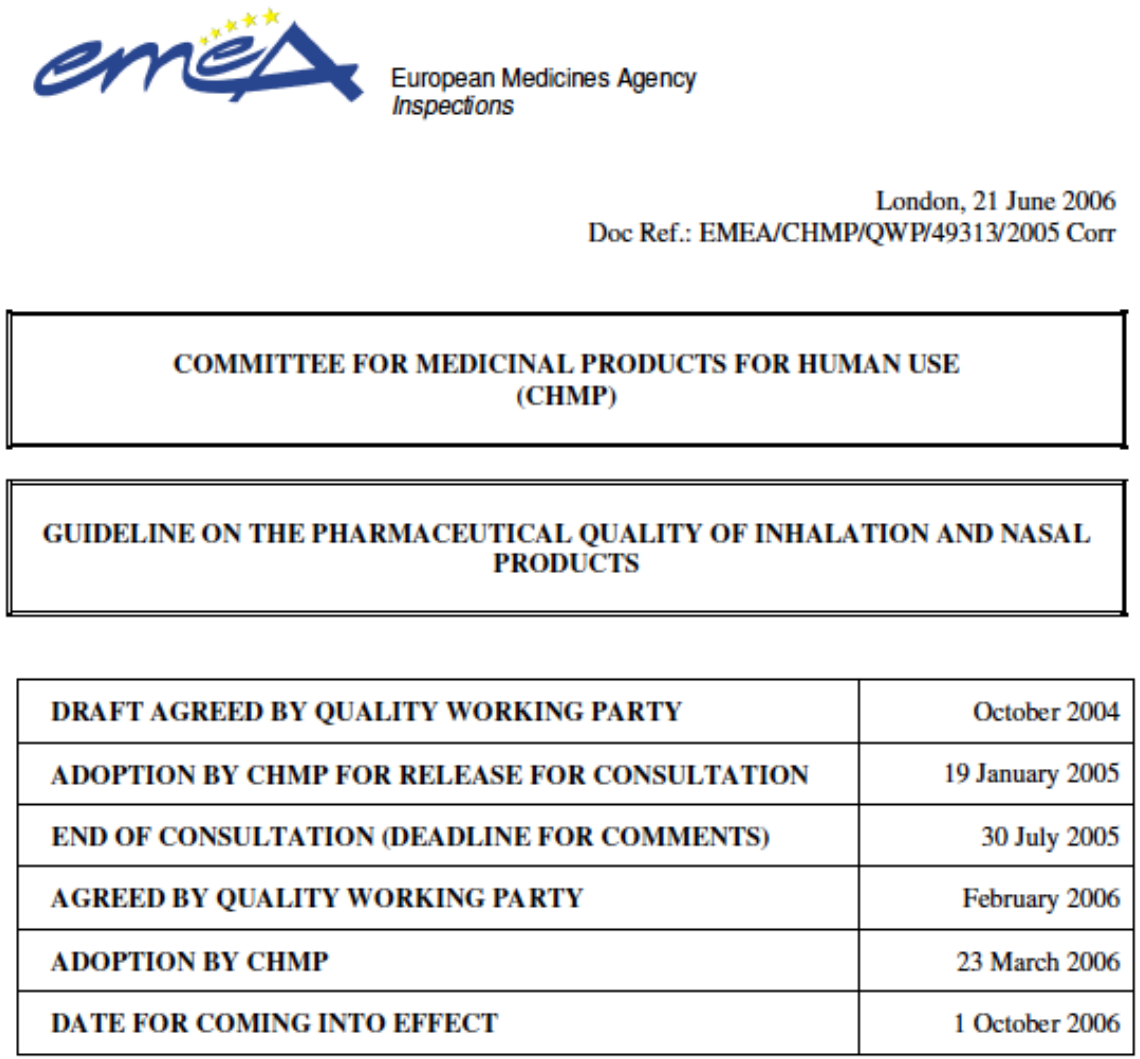
2. The batches of the test and the comparator chosen for the PK study need to be representative. What is considered as a representative batch?

OIP revision – other

- **4.2. Additional considerations**
- **4.2.1. Spacers**
  - Topic clarified
- **4.2.2. Products for nebulisation**
  - **Substantially clarified**: APSD waived under specific conditions of Q1, Q2 and physchem similarity (in line with the EMA inhalation quality gdl EMEA/CHMP/QWP/49313/2005 Corr)
  - **Wonder if it survives** – PSD requested in case of Colistimethate Sodium (powder for nebuliser solution containing only API, DE/H/6928+6929/001-002/DC and other)
- **4.2.3. Suprabioavailability**
  - **Reformulate** to match

OIP revision – Conclusion

- **OIP substantially clarifies topics** collected over the years (Q&A PKWP and Quality)
- **IVIVC "IN"**
  - Development tool, PK scaling, in vitro specification
- **Why are we using in vivo statistics for in vitro data TE?**
  - not reflecting its variability and
  - inherent properties of the methods and reference products
- **Revision of Quality guideline** for Inhalation and nasal products?



European Medicines Agency
Inspections

London, 21 June 2006
Doc Ref.: EMEA/CHMP/QWP/49313/2005 Corr

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE PHARMACEUTICAL QUALITY OF INHALATION AND NASAL PRODUCTS

DRAFT AGREED BY QUALITY WORKING PARTY	October 2004
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	19 January 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 July 2005
AGREED BY QUALITY WORKING PARTY	February 2006
ADOPTION BY CHMP	23 March 2006
DATE FOR COMING INTO EFFECT	1 October 2006

In memoriam to Dennis Sandell

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PK bioequivalence testing when between-batch variability is high: A multiple-batch proposal

A proposal that reduces the risk of false failures to show PK BE, with no serious drawbacks and without increasing the risk of wrongly concluding BE

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Thank You For Your Attention!

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