

Spanish Interpretation and Application of the OIP Guideline

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Structure of the presentation

- *Why was necessary to change the EU PtC?*
- *Decision tree for development and approval*
- *An example approved based on in vitro data only*
- *PK approach as surrogate of clinical equivalence*
- *Experience with relative potency for ICS*

*Why was necessary to change the
EU Points to Consider?*

Why was necessary to change the old EU PtC?

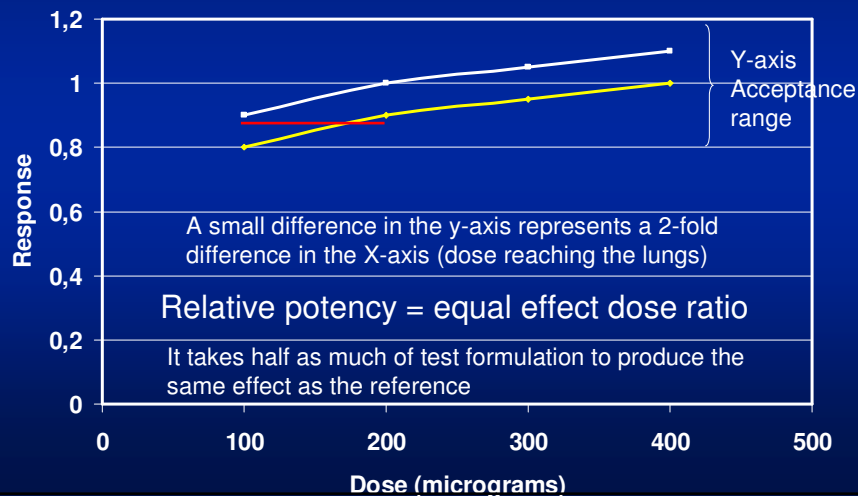
- Approvals obtained with insensitive studies
- Relative potency was not required
- Now the OIP Guideline states: *“Relative potency – defined as the ratio of the potency of the test product to that of the reference product - is one way of summarising the relationship between the dose response curves of the test and reference products. Demonstration of equivalence for at least two dose levels on the pharmacodynamic endpoint is another approach that can be used”*

Why was necessary to change the old EU PtC?

- Fortunately, the OIP Guideline also states:
- *“Efficacy: The comparison between products has to be performed in two ways.*
- *One approach is to calculate the relative potency.*
- *A second approach is to compare the results for the clinical endpoint for the test and reference products at each dose level studied.*
- *The results using both approaches should be provided.*
- *...The acceptance criteria for relative potency should lie entirely within 0.67 to 1.5.”*

What does RP mean?

Dose - Response Curve



ICS approved with insensitive trials

- Beclomethasone CFC (Becotide / Becloforte) vs. HFA (Baker Norton)
 - Milanowski et al. *Respir Med* 1999; 93:245-251
 - Paper severely criticized in literature (Pubmed)

Respir Med. 1999 Apr;93(4):245-51.
Inhaled beclomethasone (BDP) with non-CFC propellant (HFA 134a) is equivalent to BDP-CFC for the treatment of asthma.
Milanowski J, Qualtrough J, Ferrin VL.
Respiratory Clinic, Lublin, Poland.
Comment in:
Respir Med. 2000 Feb;94(2):181-2; author reply 183.
Respir Med. 2000 Feb;94(2):180-1.
Respir Med. 2000 Feb;94(2):182-3; author reply 183.
Respir Med. 2000 Feb;94(2):177; author reply 179-80.
Respir Med. 2000 Feb;94(2):177-9; author reply 179-80.

- Approved by EU assessors: according to PtC
- After approval, HPA axis suppression was higher
- Reduction of the maximum dose to overdose only mild and moderate asthmatics

In fact, it was already known

Pharmacokinetics of chlorofluorocarbon and hydrofluoroalkane metered-dose inhaler formulations of beclomethasone dipropionate

© 1999 Blackwell Science Ltd *Br J Clin Pharmacol*, 48, 866–868

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Table 1 Beclomethasone-17-monopropionate pharmacokinetic results.

	C_{max} ($\mu\text{g ml}^{-1}$)	AUC ($\mu\text{g ml}^{-1} \text{ h}$)	t_{max} (h)
BEC-HFA	2103 (586)	8603 (2571)	0.9 (0.46)
BEC-CFC	1107 (503)	5755 (3066)	1.4 (0.52)
<i>P</i> value [1]	< 0.001	< 0.005	< 0.05
90% CI [2]	1.9 fold (1.6–2.6)	1.5 fold (1.3–1.9)	

¹*P* value from test of treatment differences using an analysis of variance. ²Geometric mean fold ratio (90% CI) for BEC-HFA:BEC-CFC. Data are shown as geometric means (s.d.) for C_{max} and AUC.

And it had been confirmed

- Daley-Yates et al. (1999) *Eur Respir J*, 14(30): 196s compared Becotide CFC vs. Beclazone CFC and Beclazone HFA
- CFC formulations showed no difference
- There was a direct relationship between systemic exposure to the active metabolite and reduction in cortisol

Dose (μg)	400	800	1000	1600	2000
Test ($\text{ng}\cdot\text{h}/\text{mL}$)	2.5	6.5	7.3	10.6	14.4
Reference ($\text{ng}\cdot\text{h}/\text{mL}$)	1.6	3.3	4.6	6.2	8.6

Generic applications for β_2 agonists

- Relative potency for SABAs in North America
- The concept of Relative Potency ignored in EU
- Even “now” assessors continue to prefer a comparison in the response axis (“y” axis)
- Spain was the only country rejecting an insensitive trial with a generic LABA
- Arbitration to CMDh and commitment to avoid CHMP arbitration
- Decision of EWP to update the Guideline

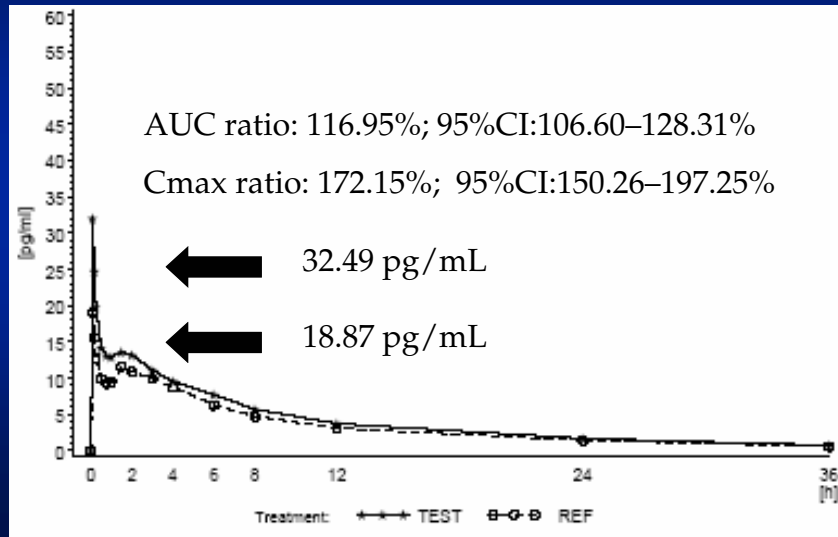
Results of the PD study

	Ratio* of AUC _{0-12h} of FEV ₁			
	mean ± SD	LS mean*	90% 2-sided CI**	p-value**
Test 6 / Test 12	0.98 ± 0.10	0.99	0.96 – 1.03	0.716
Test 6 / Ref 12	0.98 ± 0.06	1.02	0.98 – 1.06	0.342
Test 12 / Ref 12	1.01 ± 0.13	1.03	0.99 – 1.07	0.191

**Who considers that a 3% difference (up to 7%)
between test and reference is acceptable?**

**This clearly shows that the comparison of the
response of the y-axis is an inadequate methodology.
Ahrens RC. On comparing inhaled beta adrenergic
agonists. Ann Allergy 1991; 67(3):296-298.**

PK systemic exposure

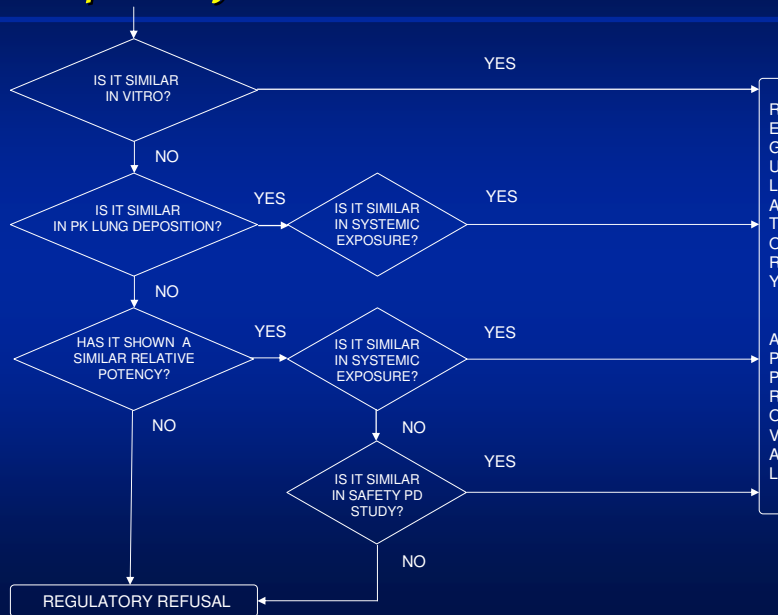


Decision tree for development and approval

The concept

Systemically acting drugs	Locally acting drug in the lungs (FDA)	Locally acting drug in the lungs (EMA)
In vitro dissolution (BCS Biowaivers)	In vitro comparison and	In vitro comparison or
PK BE study (surrogate of PD)	PK for systemic safety and	PK for systemic safety and lung deposition or
PD / Clinical study Therapeutic Eq.	Relative potency for efficacy	Relative potency for efficacy & PD safety

Proposal for decision tree in 2006



An example approved based on in vitro data only

Previous comments

- Does in vitro testing need to be relevant?
 - The more in vivo relevant the better
 - Flow profiles, realistic inlet ports
 - But it is not essential
 - In vitro dissolution: 900mL, 50 rpm, buffer
- Do we need in vitro – in vivo correlation?
 - No, as long as in vitro is more discriminative
- Do we need to predict regional deposition?
 - No, as long as it is the same in T and R, whatever it be

Previous comments

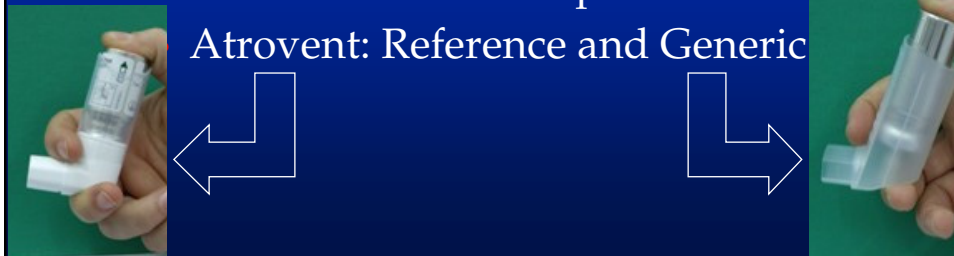
- Variability in the Reference (or test)
 - Increase sample size. No ethical problems
- Do we need to know a clinically relevant difference to define the acceptance range?
 - No, as long as very conservative
 - 15% is based in QC limit for DDU
 - Similarity factor $f_2 > 50$ used for dissolution and it lacks of clinical meaning
- Absence of data to relate in vitro and PK?
 - QVAR: Finer APSD, peripheral, PK and RP

In vitro data is sufficient to establish BE in certain cases

- Very similar device: pMDI
- APSD at multiple flow rates ~ press. Drops
 - Not relevant for pMDI but gives consistency
- In vitro data well performed
 - Pooling stages: in principle, no!
- APSD is the global test
 - DDU failure would be detected in APSD
 - The same for plume geometry, spray force
 - Temperature depends on propellant and the formulation has to be very similar
 - Relevance of physico-chemical properties of solids?

An example approved based on in vitro data only

- Ipratropium Bromide HFA pMDI
- Same composition Q_1 and Q_2
- Same valve
- Different canister shape and size
- Different mouth adaptor



EU requirements

1. The product contains the same active substance (i.e. same salt, ester, hydrate or solvate, etc.).
 - Ipratropium bromide, 20 μg
2. The pharmaceutical dosage form is identical (e.g. pMDI, non-pressurised MDI, DPI, etc.)
 - pMDI: Solution

3. The active substance is in the solid state (powder, suspension): 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.
 - Not in solid state. It is in solution
 - No possible difference

4. Any qualitative and/or quantitative differences in excipients should not influence the performance of the product (e.g. delivered dose uniformity, etc.),
 - No quantitative (Q_1) or qualitative (Q_2) difference in excipients
 - DDU, etc, is assessed in Module 3
 - aerosol particle behaviour (e.g. hygroscopic effect, plume dynamic and geometry)
 - No possible difference in hygroscopicity
 - Plume dynamic and geometry assessed indirectly by APSD
 - and/or be likely to affect the inhalation behaviour of the patient (e.g. particle size distribution affecting mouth/throat feel or "cold Freon" effect).
 - No possible difference in mouth feeling

5. Any qualitative and/or quantitative differences in excipients should not change the safety profile of the product.
 - No Q_1 or Q_2 difference in excipients
 - No possible difference in safety
6. The inhaled volume through the device to enable a sufficient amount of active substance into the lungs should be similar (within +/- 15%)
 - The volume to release the dose is so small that any patient is able to inhale it
 - This is critical in other devices (e.g. soft Mist inhaler)

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.

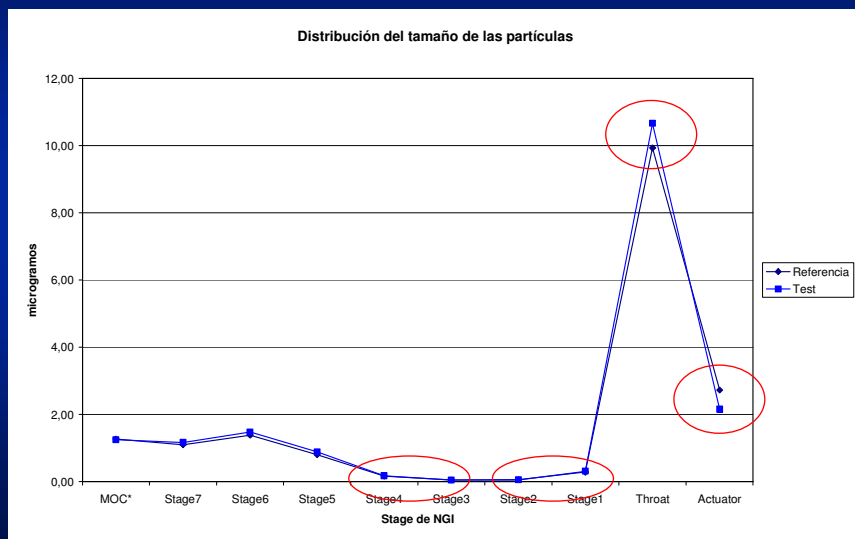
- Same handling is evident
- Small difference in shape is considered clinically irrelevant
- No spacer in the Spanish SPC



8. The inhalation device has the same resistance to airflow (within +/- 15%).
 - Not relevant for pMDI

9. The target delivered dose should be similar (within +/- 15%)
 - Parameter to be assessed in Module 3

Aerodynamic Particle Size Distribution



Aerodynamic Particle Size Distribution

- 4 batches of T and R
- 10 canister / batch
- 3 times of life cycle: start, medium, end
- 120 data for each formulation
- Firstly, analysis with no pooling
- Secondly, pooling of stages with no deposition in some determinations
- Lower amount in actuator: clinically acceptable

Aerodynamic Particle Size Distribution: no pooling

NGI	Rango de tamaño de partículas que se depositan	Test/Ref	LÍMITES 90%CI	Criterio Guía (85-115%)
Micro-orifice collector(MOC) d ₇ =	Inferior a 0,541µm	97.8%	101.2-94.4%	Cumple
Stage7 d ₆ =	0.541-0.834µm	105.5%	108.6-102.4%	Cumple
Stage6 d ₅ =	0.834-1,357µm	106.0%	108.9-103.3%	Cumple
Stage5 d ₄ =	1.357-2,299µm	109.7%	113.1-106.5%	Cumple
Stage4 d ₃ =	2.299-3,988µm	105.7%	112.7-99.2%	Cumple
Stage3 d ₂ =	3.988-6,395µm	96.4%	107.4-86.5%	Cumple
Stage2 d ₁ =	6.395-11,719µm	87.3%	97.0-78.6%	No cumple
Stage1 d ₀ =	Superior a 11.719µm	108.4%	114.7-102.3%	Cumple
Throat	--	107.4%	109.3-105.4%	Cumple
Actuator	--	80.4%	85.4-75.7%	No cumple

Aerodynamic Particle Size Distribution: unavoidable pooling

NGI	Rango de tamaño de partículas que se depositan	Test/Ref	LÍMITES 90%CI	Criterio Guía (85-115%)
Micro-orifice collector(MOC) d7=	Inferior a 0.541µm	97.8%	101.2-94.4%	Cumple
Stage7 d6=	0.541-0.834µm	105.5%	108.6-102.4%	Cumple
Stage6 d5=	0.834-1.357µm	106.0%	108.9-103.3%	Cumple
Stage5 d4=	1.357-2.299µm	109.7%	113.1-106.5%	Cumple
Stage3+Stage4	2.299-6.395µm	105.5%	113.2-98.3%	Cumple
Stage1 +Stage 2	Superior a 6.395µm	106.5%	113.1-100.4%	Cumple

PK approach as surrogate of clinical equivalence

The old myth of useless PK

PK is useless in comparing inhalation products because:

- Systemic levels are not detectable
- Systemic levels also reflect GI absorption
- Systemic levels do not reflect lung concentrations
- Systemic levels are different in patients and healthy volunteers
- There is no PK/PD relationship

Br. J. clin. Pharmac. (1992), **33**, 439–444

Effects, side effects and plasma concentrations of terbutaline in adult asthmatics after inhaling from a dry powder inhaler device at different inhalation flows and volumes

T. ENGEL, B. SCHARLING, B. SKOVSTED & J. H. HEINIG
Allergy Unit TTA 7511, National University Hospital, Tagensvej 20, DK-2200 Copenhagen, Denmark

- 1 The efficacy of a metered dose inhaler (MDI) is highly dependent on the mode of inhalation. The relatively high built-in resistance in the Turbohaler® (TBH), a new dry powder inhaler device for inhalation of terbutaline sulphate and budesonide, reduces the flow during inhalation. We compared five different modes of inhalation using the terbutaline TBH in 10 stable asthmatic subjects, who were tested on 5 consecutive days. ←
- 2 Measurement of 10 different parameters of pulmonary function indicated that the full bronchodilatory effect of an inhaled dose was already achieved at 5 min after the inhalation. Inspiratory flows through the TBH varying from 34 to 88 l min⁻¹ resulted in comparable bronchodilation, and a previous exhalation to residual volume proved of no value. However, if, prior to inhalation, an exhalation through the device was performed, a substantially reduced effect was seen. ←
- 3 Reducing the inspiratory flow to approximately 34 l min⁻¹ produced slightly reduced side effects and lower plasma terbutaline concentrations. ←

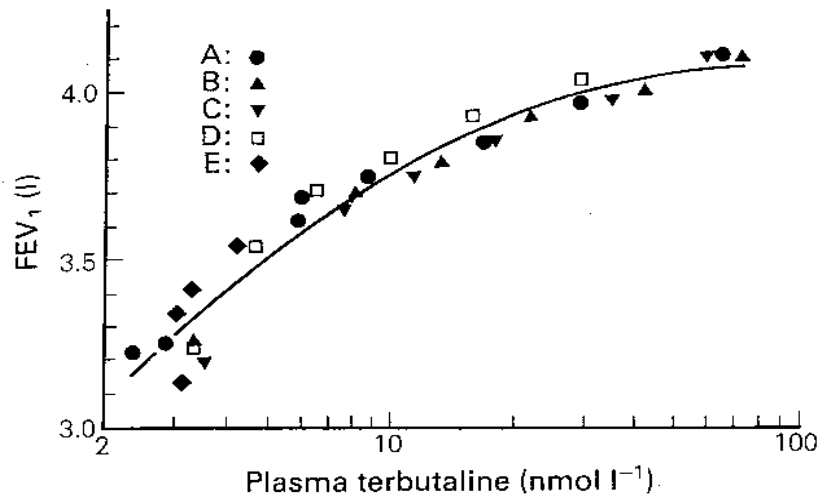


Figure 6 Bronchodilatation (FEV₁) following inhalation of different doses of terbutaline from the TBH in relation to concomitant plasma terbutaline concentration in 10 adult asthmatics. A–E: Inhalation techniques on days A–E (see Figure 1 for further explanation).

The new excuses to complicate the development of generics

- Buccal absorption is also possible, not only gut absorption
 - Yes, but it has not been described for existing products
 - It can be verified very easily in an PK experiment with a buccal solution
- Active charcoal does not block GI absorption completely
 - A small absorption can be ignored like pre-dose values lower than 5% C_{max} in conventional BE
 - AUC(0-30min) and C_{max}(0-30min) no affected by GI absorption
 - Several drugs have complete first pass effect: Fluticasone and Ciclesonide

The new excuses to complicate the development of generics

- Finer APSD and more peripheral not always higher Cmax
 - Esposito-Festen JE et al, *BJCP* 2007;64:328–334 measured the metabolite and the parent has to be measured
 - It was a monodisperse aerosol. Not a real pMDI
 - Probably so much peripheral, no lung metabolism
- PK sensitivity is lower for more soluble and rapidly dissolving drugs
 - If it has worked with budesonide and beclomethasone, it will work better for fluticasone

BDP HFA with vs. without spacer: Parent is superior, metabolite is not

- Parent:
 - Cmax: 181
 - (90%CI: 138-237)
 - AUC(0-30): 185
 - (90%CI: 144-239)
 - AUCt: 188
 - (90%CI: 146-241)
- Metabolite:
 - Cmax: 144
 - (90%CI: 119-175)
 - AUC(0-30): 141
 - (90%CI: 121-164)
 - AUCt: 88
 - (90%CI: 79-98)

Parameter	T1 With charcoal	T2 With spacer	R Standard actuator	% PE T1 vs. R	% PE T2 vs. R	90% CI T1 vs. R	90% CI T2 vs. R
C _{max} (pg/mL)	3033.1e1448.4	5454.9e3197.1	3822.3e1449.9	100	181	83 - 142	138 - 237
AUC ₀₋₃₀ (pg/mL·h)	435.2e204.2	781.0e439.8	399.5e199.4	110	185	85 - 142	144 - 239
AUC _{0-t} (pg/mL·h)	445.0e213.3	803.3e449.6	407.8e204.9	110	188	86 - 141	146 - 241
AUC _{0-∞} (pg/mL·h)	452.6e217.6	826.6e460.0	450.0e207.7*	113**	196**	87 - 147	150 - 255
T _{max} (h)	0.08 (0.08-0.08)	0.08 (0.08-0.12)	0.08 (0.08-0.12)	NC	NC	NC	NC
t _{1/2} (h)	0.16e0.14	0.42e0.37	0.16e0.09**	NC	NC	NC	NC

Source: Synopsis table CP04 study report (5.3.3.1.3)
 *N=10; NC: not calculated; values are arithmetic means ± SD, except T_{max}: median (range); PE: point estimate calculated as ratio of geometric means test/reference × 100 or ** as ratio of geometric least squares means test/reference × 100

Parameter	T1 With charcoal	T2 With spacer	R Standard actuator	% PE T1 vs. R	% PE T2 vs. R	90% CI T1 vs. R	90% CI T2 vs. R
C _{max} (pg/mL)	775.0e292.7	1138.9e495.6	771.6e288.7	100	144	83 - 122	119 - 175
AUC ₀₋₃₀ (pg/mL·h)	271.3e87.9	402.2e135.2	292.3e126.3	96	141	82 - 112	121 - 164
AUC _{0-t} (pg/mL·h)	1559.2e565.3	2539.6e726.9	2900.8e893.4	53	88	48 - 59	79 - 98
AUC _{0-∞} (pg/mL·h)	1733.9e613.4	2841.2e750.3	3234.0e973.7	53	89	48 - 59	79 - 99
T _{max} (h)	0.08 (0.08-0.28)	0.10 (0.08-0.50)	0.08 (0.08-0.75)	NC	NC	NC	NC
t _{1/2} (h)	3.70e0.77	4.23e1.47	3.84e0.60	NC	NC	NC	NC

Source: Synopsis table CP04 study report (5.3.3.1.3)
 NC: not calculated; values are arithmetic means ± SD, except T_{max}: median (range); PE: point estimate calculated as ratio of geometric means test/reference × 100; CI: confidence interval

The new excuses to complicate the development of generics

- There is no equilibrium between lung and plasma because efficacy does not depend on systemic concentrations
 - Equilibrium does not mean equal concentrations.
 - Fluticasone distributes to the tissues.
 - After inhalation equilibrium is reached with more concentrations in the lung and less in blood.
 - After oral administration equilibrium is reached with more concentration in other tissues than in the lungs
 - It is matter of distribution! It has nothing to do with equilibrium!
 - That is why with the same plasma concentrations the oral dosing does not give the same efficacy than the inhaled one
 - Do not misinterpret the paper by Lawrence M et al. 1997
 - Am J Respir Crit Care Med. 1997;156:744–751

The new excuses to complicate the development of generics

- Two dry powder inhalers of budesonide showed
 - PK Bioequivalence (Persson et al. 2008. Curr Med Res Opin. 24(5) 1511-517) and
 - Are claimed not to be equivalent clinically based on Kerwin et al. 2008. Curr Med Res Opin. 24(5) 1497-510
- This was not a therapeutic equivalence study
 - “These studies were not designed to test equivalence or noninferiority between the active products” according to the abstract of the paper
- One out of eight arms was not able to show superiority to placebo
 - Adults and children at two different posologies with two devices (2x2x2=8)
 - But it was statistically superior to placebo in the Per Protocol analysis
 - The difference between the two devices at the low dose posology in adults was 0.08 L in predicted FEV₁
 - This is not considered clinically relevant according to a delta of 0.2 or 0.23 (Santanello et al. 1999. Eur Respir J. 14(1):23-27)
- This is not enough to consider them equivalent, but it is also not proof that they are not equivalent

The basic questions

- Do the systemic concentrations for an orally inhaled topically acting drug reflect those at the site of action?
 - Yes, because the drug reaching the site of action is later absorbed
- Is the rate (C_{max} and T_{max}) and extent (AUC) of availability in the plasma directly related to the rate and extent of drug available at the site of action?
 - It is a mirror of what just happened in the site of action like the PD effect (deposition, absorption into cell, binding to receptor, transduction of the signal ...)
 - But the effect is insensitive to differences in dose and PK is not. PK is dose-proportional

Can PK lung deposition studies indicate deposition pattern?

- If the particle size distribution is not very different, the deposition pattern is not altered. The dose (AUC) reaching the lung is the only important thing
 - Chrystyn H. Is total particle dose more important than particle distribution? *Respir Med* 1997; 91 Suppl A:17-19
 - Selroos O, Pietinalho A, Riska H. Delivery Devices for Inhaled Asthma Medication. *Clin Immunother* 1996; 6:273-299

Can PK lung deposition studies indicate deposition pattern?

- If the PSD is different the deposition is altered, but also the extent.
 - Usmani OS, Biddiscombe MF, Nightingale JA, Underwood SR, Barnes PJ. Effects of bronchodilator particle size in asthmatic patients using monodisperse aerosols. *J Appl Physiol* 2003; 95:2106-2112
 - Usmani OS, Biddiscombe MF, Barnes PJ. Regional Lung Deposition and Bronchodilator Response as a Function of β_2 -agonist Particle Size. *Am J Respir Crit Care Med* 2005

Can PK lung deposition studies indicate deposition pattern?

- In addition, the C_{max} is more sensitive than the AUC to detect different sites of deposition
 - Benson MK, Curry SH, Mills GG, Hughes DT. Uptake of disodium cromoglycate in obstructive airways disease. *Clin Allergy* 1973; 3:389-394
 - Neale MG, Brown K, Hodder RW, Auty RM. The pharmacokinetics of sodium cromoglycate in man after intravenous and inhalation administration. *Br J Clin Pharmacol* 1986; 22:373-382
 - Kohler E, Sollich V, Schuster-Wonka R, Huhnerbein J. Lung deposition in cystic fibrosis patients using an ultrasonic or a jet nebulizer. *J Aerosol Med* 2003; 16:37-46.
 - Kohler E, Sollich V, Schuster-Wonka R, Huhnerbein J, Jorch G. Does wearing a noseclip during inhalation improve lung deposition? *J Aerosol Med* 2004; 17:116-122

Can PK lung deposition studies indicate deposition pattern?

- Products with known difference in the lung deposition pattern

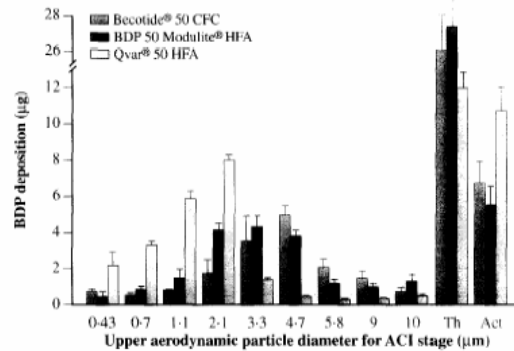


FIGURE 6. Comparative *in-vitro* particle size distribution for three BDP 50 µg pMDIs: Becotide® CFC suspension, Modulite® HFA solution, and Qvar® HFA solution.

Modulite CFC and HFA vs. QVAR

- The more peripheral deposition, the higher C_{max}

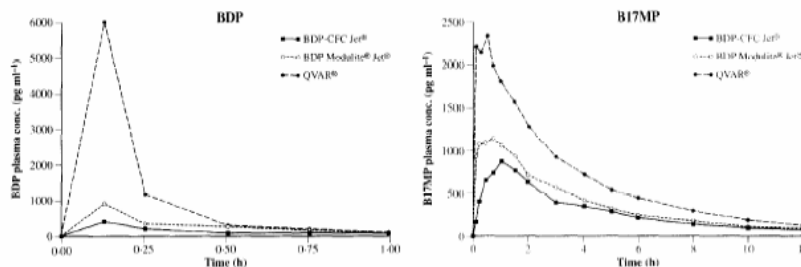


FIGURE 4. BDP and B17MP median plasma levels in 12 healthy volunteers after a 1000 µg dose.

PD vs. PK

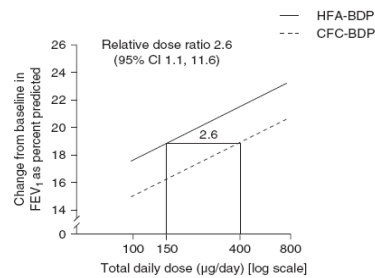


Fig. 3. The results of the regression analysis for change from baseline in forced expiratory volume in 1 second (FEV₁) percent predicted at week 6 are shown by treatment group. The shift is quantified by the relative dose ratio of 2.6, which indicates that it would require 2.6-fold the dose of chlorofluorocarbon beclomethasone dipropionate (CFC-BDP) to achieve the same change from baseline in FEV₁ as percent predicted with hydrofluoroalkane (HFA)-BDP (reproduced from Busse et al.¹⁷⁹ with permission from Elsevier).

Busse WW, Brazinsky S, Jacobson K, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *J Allergy Clin Immunol* 1999; 104: 1215-22

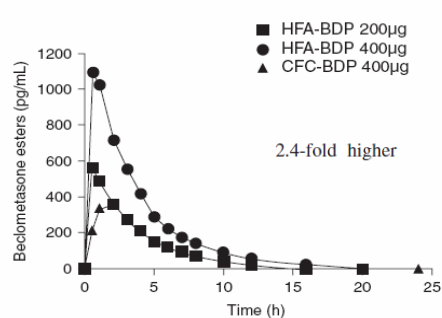


Fig. 2. Mean serum concentrations of beclomethasone esters following inhalation of hydrofluoroalkane beclomethasone dipropionate (HFA-BDP) 200µg, HFA-BDP 400µg and chlorofluorocarbon (CFC)-BDP 400µg (reproduced from Harrison et al.,¹⁸⁴ with permission).

Harrison LJ, Soria I, Cline AC, et al. Pharmacokinetic differences between chlorofluorocarbon and chlorofluorocarbon-free metered dose inhalers of beclomethasone dipropionate in adult asthmatics. *J Pharm Pharmacol* 1999; 51: 1235-40

Consensus to be reached

- PK more discriminative
 - For hydrophilic and lipophilic drugs
- PK as a mirror of lung deposition
 - No evidence against
 - Evidence in favour: QVAR...
- HV in asthma and COPD instead of Patients
 - Not for cystic fibrosis
- Acceptance range: clinical relevance?
 - It only needs to be conservative enough
- Charcoal block limitations
 - Some GI absorption acceptable as 5% of C_{max}
 - Levels in first 30 minutes: salbutamol
 - Cases with negligible GI absorption: Fluti., Cicles.

Consensus to be reached

- Paediatric patients
 - Unethical? almost in all paediatric develop.
 - Impractical? Better than clinical studies
 - Short studies
 - Blood sampling for cortisol?
- Acceptable for all ages and severities
- Dose reaching the lungs: AUC
- Pattern of deposition: C_{max} and T_{max}
- Scaling: case by case
 - C_{max} and T_{max} more important
- Proportional formulations: T vs. R at all strengths

Surrogates of Therapeutic Equivalence

- Barbara M. Davit, Office of Generic Drugs. CDER/FDA
- Bioequivalence Methods for GI Locally-Acting Drugs in AAPS Workshop on BE, BCS, and Beyond. May 21 - 23, 2007
- <http://www.aapspharmaceutica.com/meetings/files/90/23/Davit.pdf>
- Colestipol HCl tablets: in vitro study. Binding bile, in vitro & Local AE
- Sucralfate tablets: clinical study. Minimal systemic conc. & Local AE
- Misoprostol tablets: PK study. Well-absorbed & Systemic AE
- Sulfasalazine tablets: PK study. Well-absorbed in the site of action
- Mesalamine rectal suspension: PK study. Absorption in site of action

PK already employed to show

- **Radiolabel does not alter lung deposition**
 - Newman, S., A. Salmon, R. Nave, and A. Drollmann. 2006. High lung deposition of ^{99m}Tc-labeled ciclesonide administered via HFA-MDI to patients with asthma. *Respir.Med.* 100:375-384.
- **Influence of spacer on lung deposition**
 - Drollmann, A., R. Nave, V. W. Steinijans, E. Baumgartner, and T. D. Bethke. 2006. Equivalent pharmacokinetics of the active metabolite of ciclesonide with and without use of the AeroChamber Plus spacer for inhalation. *Clin Pharmacokinet.* 45:729-736.
- **Influence of disease on lung deposition**
 - Nave, R., K. A. Gunawardena, K. Zech, and T. D. Bethke. 2006. Pharmacokinetic disposition of inhaled ciclesonide and its metabolite desisobutyryl-ciclesonide in healthy subjects and patients with asthma are similar. *Int.J.Clin Pharmacol Ther* 44:1-7.

*Experience with relative potency for
ICS*

First possible design

Ahrens model (Cross-over design, FEV₁)

- Ahrens RC, Teresi ME, Han SH et al. Asthma stability after oral prednisone: a clinical model for comparing inhaled steroid potency. *Am J Respir Crit Care Med* 2001; 164(7):1138-1145
- Ahrens RC, Hendeles L, Teresi ME et al. Stability of asthma following maximization of lung function with a high-dose inhaled corticosteroid (ICS) burst: a more precise method for comparing clinical potency of ICS. *J. Aerosol Med.* 16[2], 197. 2003
- Ahrens RC, Hendeles L, Teresi M et al. Relative potency of beclomethasone propionate (BDP), delivered by HFA-MDI, and fluticasone propionate (FP) delivered by Diskus. *Eur. Respir. J.* 22[Suppl 45], 236S. 2003

Second possible design

Lipworth model (Cross-over, PD₂₀)

- Lipworth BJ, Sims EJ, Das SK et al. Dose-response comparison of budesonide dry powder inhalers using adenosine monophosphate bronchial challenge. *Ann Allergy Asthma Immunol* 2005; 94(6):675-681
- Fardon TC, Burns P, Barnes ML et al. A comparison of 2 extrafine hydrofluoroalkane-134a-beclomethasone formulations on methacholine hyperresponsiveness. *Ann Allergy Asthma Immunol* 2006; 96(3):422-430

Third alternative

FDA proposal for eNO (Cross-over)

- It was already used as secondary variable by Lipworth BJ, Sims EJ, Das SK et al. Dose-response comparison of budesonide dry powder inhalers using adenosine monophosphate bronchial challenge. *Ann Allergy Asthma Immunol* 2005; 94(6):675-681
- It would be possible to compare eNO and PD₂₀
 - While 100 µg of QVAR significantly suppressed FE_{NO}, 400 µg of QVAR is required to significantly attenuate methacholine airway hyper-responsiveness

4th alternative: Sputum Eosinophilia What if the placebo is ignored?

Eosinophilic bronchitis in asthma: A model for establishing dose-response and relative potency of inhaled corticosteroids

Margaret M. Kelly, MBChB,^a Richard Leigh, MBChB, PhD,^a Lata Jayaram, MBChB,^a Charlie H. Goldsmith, PhD,^b Krishnan Parameswaran, MD, PhD,^a and Frederick E. Hargreave, MD^a Hamilton, Ontario, Canada (J Allergy Clin Immunol 2006;117:989-94.)

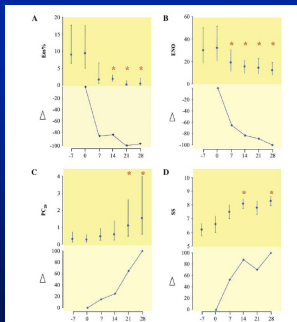


FIG 1. A, Percent sputum eosinophils (Eos%); B, eNO (ppb); C, Methacholine PC₂₀ (mg/mL); D, Symptom score (SS). Solid circles, geometric mean; vertical lines, SE; solid diamonds, change from baseline expressed as % of total change; □, *P < .05 compared with baseline.

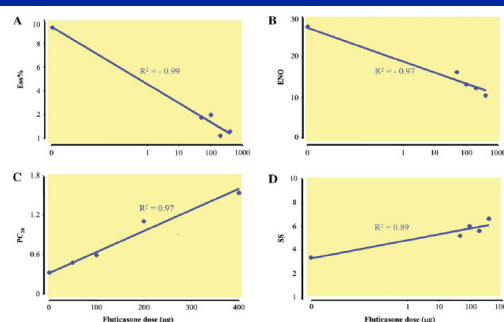


FIG 2. Outcome variables versus dose. (A) Sputum eosinophils (%), (B) eNO (ppb), (C) methacholine PC₂₀ (mg/mL, expressed as geometric mean), and (D) symptom score (SS).

Combination products (ICS + LABA)

- A study for each component
- At least 2 doses with the lowest strength
- Single dose study for LABA. ICS effect is negligible
- ICS study model with a specific endpoint for ICS: inflammation
 - eNO
 - Sputum eosinophils
 - If no specificity: give the same amount of LABA with an additional device to compensate



*Thank you very
much for your
attention*