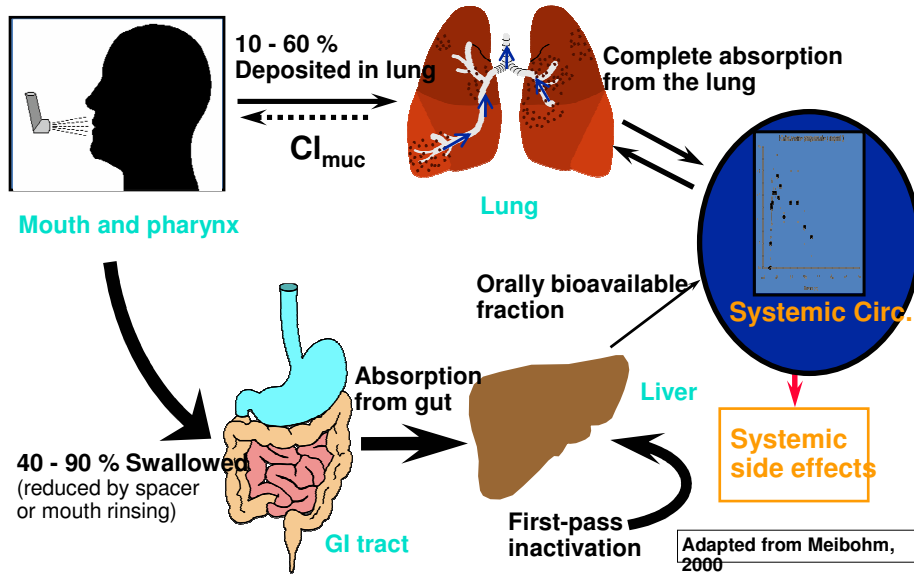


Some unresolved issues in the use of PK for equivalence of OIP (with Focus on European Guidelines)

Günther Hochhaus (*University of Florida, USA*)

Topics related to Bioequivalence



- PK is an easy way to provide in vivo information
 - Advantage:
 - no need for showing in vitro/ in-vivo correlations
 - more sensitive than clinical studies
 - able to answer main key questions relevant for bioequivalence

BE of Inhalation Drugs

• LOCAL EFFECTS

- How much is avail. to Lung?
 - Considers mucociliary clearance
- Where is drug deposited?
 - (central /peripheral)
- How long does drug stay in the lung? (residence time)

• SYSTEMIC SIDE EFFECTS

- How much is absorbed? (Safety)

BE of local effects:

- In-vitro tests, scintigraphy
- Pharmacokinetics
- Clinical studies

PK and EMEA

- Pulmonary [PK based] deposition studies are designed as double blind, crossover studies and should be carried out using a clinically relevant dose(s) and strength(s) of the product (which may be determined from the *in vitro data*). *These studies should be performed in the intended patient population.*
- In children pulmonary deposition studies are not appropriate. Pharmacokinetic studies as a surrogate for efficacy **only imply efficacy**, they increase the burden on the child and have insufficient advantages over pharmacodynamic and/or clinical studies in the assessment of therapeutic equivalence in children to warrant their use. Imaging studies in children are also not appropriate.

Design of PK studies

- In accordance with the standard accepted methods of assessment of bioequivalence the maximum concentration (C_{max}), the area under the curve (AUC) and **the time to C_{max} (T_{max})** should be compared.
- Equivalent pulmonary deposition and equivalent systemic safety of two inhaled products may be concluded if the 90 % confidence interval for each parameter lies within the acceptance range of 0.8 to 1.25. However, in some circumstances, for example, **for active substances with a narrow therapeutic window, the 90% CI** may require tighter limits when assessing systemic safety. Conversely, for products with high variability it may be acceptable if certain conditions are satisfied to widen the acceptance range for C_{max} to 0.75 to 1.33 (see CHMP/EWP/QWP/1401/98 Rev.1 for further details).
- If pharmacokinetic studies are carried out **in children** for the assessment of systemic safety the active substance should be measured in plasma.

EMEA

- PK Studies:
 - For evaluating pulmonary deposition
 - A pharmacokinetic study designed to assess pulmonary deposition, has to be able to exclude absorption of the active moiety from the gastrointestinal tract (for example by using **charcoal** blockade).
 - However it may be possible for substances with negligible gastrointestinal absorption that the pharmacokinetic study designed to assess pulmonary deposition may be sufficient in the assessment of therapeutic equivalence.
 - In some cases equivalent pulmonary deposition demonstrated through pharmacokinetic studies in combination with safety data (for example, data from a systemic safety pharmacokinetic study, see section 6.1.1 below) might be considered as sufficient demonstration of therapeutic equivalence, if justified. However, in general, therapeutic equivalence must be demonstrated by means of appropriate pharmacodynamic and/or clinical studies.
 - For evaluating systemic safety
 - In the investigation of systemic safety total systemic exposure has to be measured in the intended patient population and therefore the study must include the measurement of that amount of the active moiety absorbed through the lung and the gastrointestinal tract

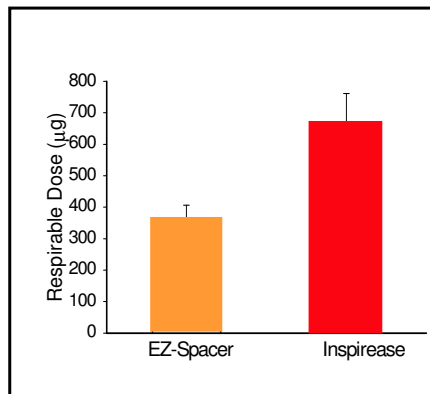
EMEA

- If the product for which a new marketing authorisation is sought fails to show equivalence to the reference product based on *in vitro* data (see section 5.2 above), one way to demonstrate equivalent efficacy may be through a comparison of pulmonary deposition.
*Comment: in vitro- in vivo correlations are almost non-existing.
in vivo studies should always be included.*
- Pharmacokinetic studies may have some advantages, even though they provide data indirectly from plasma or urine: Pharmacokinetic studies are **easier to perform**, they are safer due to the lack of radiation, they avoid the risk of altering the formulation during radio-labelling and they can **demonstrate linear dose-response** relationships more easily.
- In addition, pharmacokinetic studies measure total systemic exposure (for assessment of safety), and pulmonary absorption (for assessment of pulmonary deposition and efficacy) can be separated from gastrointestinal absorption. Pharmacokinetic studies may even take into account active substance removed by **mucociliary clearance**.
- Limitations with pharmacokinetic studies include their **inability to differentiate the distribution of drug within the different zones of the lung** following inhalation and in some cases plasma/urinary concentrations are not measurable at clinical doses or are near the lower limit of quantification such that results may be highly variable.
 - Has this been shown for clinical studies??
 - Also, PK might be able to differentiate between c/p deposition differences.

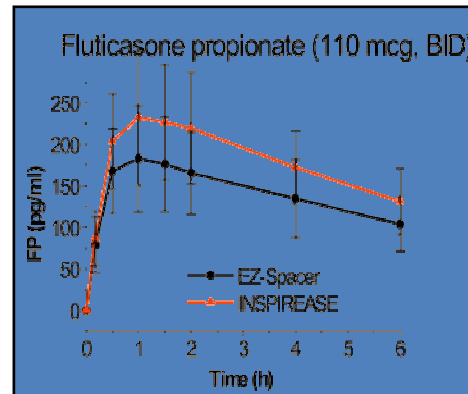
Topics

- Patient- Volunteers
- Adults +/- children (spacer)
- T_{max}
- C/p ratio
- Narrow therapeutic drugs (smaller window)
- Combination products

In-vivo/in-vitro Correlation



50 % Difference in RD



20% Difference in AUC and C_{max}

Asmus, Hendeles et al.

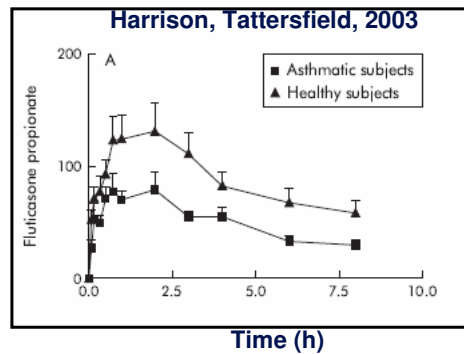
PK based AUC's capture additional factors than just "respirable dose"

Asthmatics or Healthy volunteers?

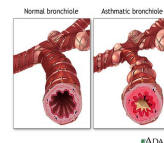
- PK is a tool (living cascade impactor)
- System (healthy, asthmatics) should detect relevant differences in formulation/devices with highest resolution
- The higher central deposition (asthmatics), the lower power to detect differences in formulation
- Differences in lung function across asthmatics will increase variability
- This argues for studies in healthy volunteers
 - What flow rates should be used?
- Combination (Healthy/asthmatics) might improve power to detect differences.

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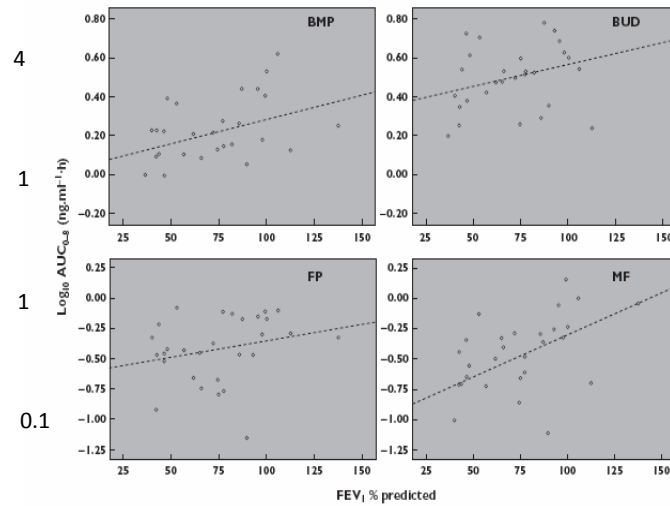
What happens if one switches to asthmatics?



- Dose to lung is similar for Asthmatics and Healthy (Edsbaecker, 2008)
- C/P ratio has to differ to explain difference in AUC
- 50/50 (typical value) in healthy to 90/10 in asthmatics
- Deposition in asthmatics is more central



Lung function determines for most ICS s
how much drug is available to the Patient's lung



Mortimer et al., 2006

Suggestion

- AUC depends on lung function
- Use of asthmatics with differing lung function will increase variability
- Healthy volunteers should be used, as PK studies should only identify potential differences between Test and reference product (living cascade impactor)

Adults vs Children

- What is the likelihood that a generic shown in adults and in *in vitro* studies to be bioequivalent with Reference product, will not be equivalent in children.
- Are bioequivalency studies necessary in children
- Are spacer studies necessary??

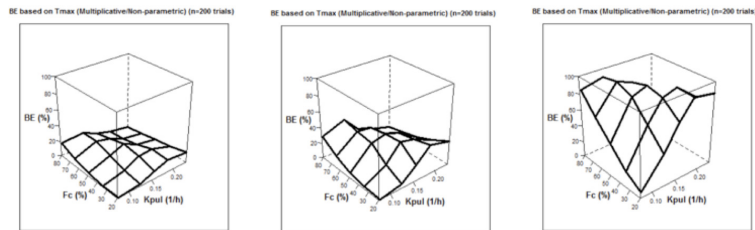
t_{max}

Reference	Test	Difference (%)	C_{max}	t_{max} parametric	t_{max} Non-parametric	AUC
K_a [1/h]	K_a [1/h]	K_a [1/h]	(%)	(%)	(%)	(%)
0.167	0.1	-40.12	0	30.5	4	0.5
0.167	0.13	-22.16	5	58	6	35
0.167	0.167	0.00	97	74.5	18.5	98
0.167	0.21	25.75	6.5	58.5	9.5	66.5
0.167	0.25	49.70	0	33	3.5	13.5
0.167	0.3	79.64	0	10	1.5	0.5

- C_{max} is the most sensitive parameter (better than MRT, MAT, not shown)
- Use of t_{max} as proposed by EMA does not make sense

BE-Simulations

T_{\max} (B)



Wilcoxon's sign rank test

C/P Ratio

- PK is highly suitable to answer:
- Is dose available to the lung equivalent?
- Is the pulmonary residence time equivalent?
- C/P ratio?
- slow dissolving formulations: mucociliary clearance
- Fast dissolving formulations: C_{\max} ,

Simulations: AUC affected by C/P ratio

drug is slowly dissolving, such as FP

200 Simulations (same Dose)

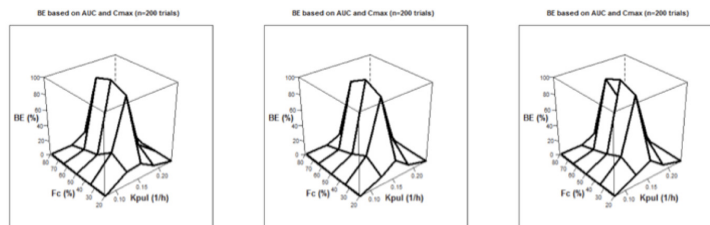
	Brand	Generic	Generic	Generic
C/P Ratio	45/55	45/55	63/37	22/78
Variability	30%	30%	30%	30%
N	30	30	30	30
Bioequivalent Trials*		82%	6%	6%

* % Trials with CI within 80-125%

—————→ • AUC is sensitive to C/P ratio

BE Simulations (C/P)

AUC/C_{max}



PK of faster dissolving Drugs

	Submicron Budesonide (MAP) 0.5 mg/ml	Pulmicort Respules (0.5 mg/ml)
Fine Particle Mass	145 ± 8	69 ± 6
Ultrafine Particle Mass	49 ± 2	10 ± 1
		Bosco, Uster (2007)

	C _{max} (± SE) pg/ml	t _{max} min	AUC ± SE ng*min/ml
Budesonide Respules	255 ± 80	9.1 ± 0.9	29.1 ± 8.5
Submicron Budesonide	388 ± 121*	3.5 ± 1.0 *	21.2 ± 6.6 *

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Differences in regional distribution are reflected in PK

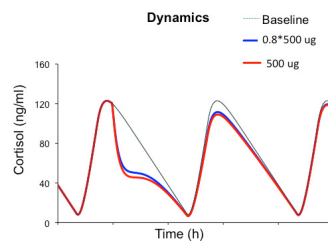
Conclusion

- PK studies are suitable to make bioequivalence decisions
 - » How much, where, and for how long?
- Personnel Statement:
 - » PK studies should be the cornerstone of any BE study for ICS

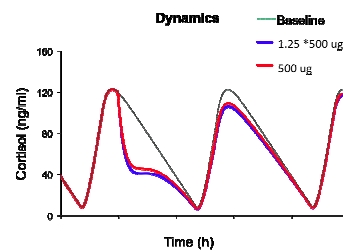
Narrow therapeutic window drugs. (e.g. corticosteroids)

- Smaller window (<0.8-1.25)
- Probably incorporated because of glucocorticoids

Cortisol Suppression



25.0% **28.5%**



32.2% **28.5%**

It does not seem to make sense to narrow the limits.

Combination Products

- LABA show relatively steep dose response
- Glucocorticoids don't.
- Differential evaluation of components with clinical approaches is difficult
- Using in-vitro/PK for glucocorticoids And clinical studies for LABA's might be a solution.

Conclusion

- EMA is on the right track for using PK for Bioequivalence decisions of inhalation drugs
- Some fine tuning is necessary
- Consensus is necessary as to what PK can delivery.