

Experience with the OIP Guideline – A Clinical Perspective from the UK on PK and Equivalence Studies

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Revised OIP guideline

- In effect since August 2009
- Stepwise approach to demonstrate equivalence
 - Step 1. *In vitro* data
 - Step 2. Lung deposition models (PK / scintigraphy)
 - Step 3. Therapeutic effect / pharmacodynamic models

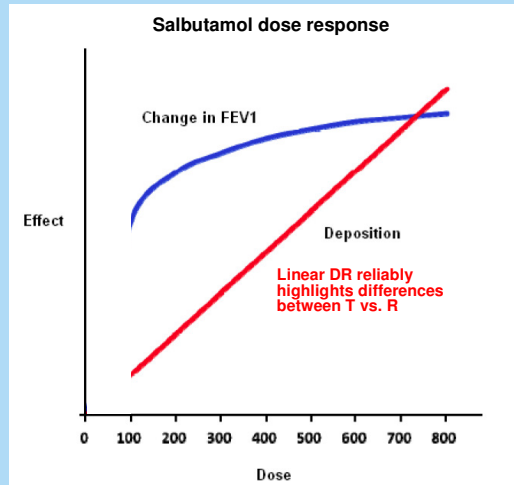
If equivalence confirmed at steps 1 or 2, may be no need for further data

<http://www.ema.europa.eu/htms/human/humanguidelines/efficacy.htm>

Rationale for lung deposition studies (PK / scintigraphy)

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Highly sensitive models



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Rationale for lung deposition studies (PK / scintigraphy)

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- Substantial literature base
- Have demonstrated significant differences:
 - Between devices
 - At different flow rates
 - With different respiratory manoeuvres
 - With different respirable dose / fine particle dose
 - With different particle sizes
 - Between patients and healthy volunteers
 - With different excipients

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Relevance of PK

- OIP PK an indirect, 'after-the-effect' assay
- However, BE for non-OIPs frequently does not measure target organ drug levels, e.g., opioids
- PK sensitive to differences of $\leq 20\%$. Less useful to determine BE than bioassays typically sensitive to differences of $\sim 400\%$?
- Where PD dose response exists, PK detects differences, i.e., deposition relates to clinical effect^{1,2}
- No studies have simultaneously demonstrated PD differences but equivalent PK

1. Pauwels, Eur Resp J 1997
2. Selroos, Clin Immunother 1996

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UK experience with OIP PK

- Confirms highly discriminative nature of PK
- OIP BE is a high, not low, hurdle
- Why is it difficult?
 - Variability of inhalation manoeuvres
 - Variability of T/R

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Why is demonstration of BE on PK difficult?



1) Variability of inhalation manoeuvres

Reported ISV for salbutamol (2 to 5 periods in each study)

Device	Intrasubject coefficient of variation (%)	
Evohaler MDI ¹	8.2%	University of Bradford, UK – likely highly trained volunteers, experienced with inhalation studies
Evohaler MDI ²	6.1%	
Evohaler MDI ³	10.1%	
Easibreathe breath actuated MDI ³	7.1%	Subjects trained only at start of period 1 (of 5 periods)
Easibreathe breath-actuated MDI ⁴	35.9%	
Accuhaler DPI ⁴	40.4%	
Turbuhaler DPI ⁴	42.4%	
Evohaler MDI ⁴	52.0%	
Evohaler MDI + Volumatic ⁴	31.8%	

1. Hindle, Br J Clin Pharm 1992
2. Hindle, Thorax 1994
3. Tomlinson, Br J Clin Pharm 2003
4. Aswanis, J Aerosol Med 2004

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Why is demonstration of BE on PK difficult?



Generic vs Reference salmeterol-fluticasone MDI BE study data

- Individual data for 8 subjects (of 52) with highest and lowest salmeterol T/R AUC_{0-t} ratios

	Subject	Individual T/R AUC _{0-t} ratio	
		Salmeterol	Fluticasone
Highest	1	390%	368%
	2	374%	194%
	3	342%	109%
	4	285%	153%
Lowest	5	53%	31%
	6	51%	34%
	7	49%	44%
	8	41%	32%

Correlation coefficient = 0.89

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How to address inhalation variability ?

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- ↑ sample size addresses high intrinsic ISV but not differences in amount of drug inhaled due to unreliable inhalation
- Use method to standardise / monitor inhalation manoeuvre, e.g., inhalation profile recorder. Should:
 - Variability
 - Reduce type 2 error

Not routinely seen as yet in registration studies

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Why is demonstration of BE on PK difficult?

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Variability of reference (and test) OIP

- Specifications for R product allow variations in delivered dose of e.g., 20 - 35%
- Given, *inter alia*, methodological issues related to quantification, specifications for FPD allow variation between R batches of, e.g., 25 – 45%
- Such variability / specification range is not a standard feature of medicinal product delivered e.g., by oral route
- Clearly variations in R FPD have huge implications for likelihood of demonstrating BE in a PK study
- *In vitro* comparisons may be less affected by such variability as mean *in vitro* parameters typically derived from several T & R batches – vs. 1 batch of T & R in BE

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Why is demonstration of BE on PK difficult?

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Richardson CH et al, Pharm Res 2007

- Urine PK
- Single-dose, 4-way crossover study
- 12 healthy subjects
- Four different salbutamol formulations (200 µcg) via Clickhaler™ DPI

		Formulation 1	Formulation 2	Formulation 3	Formulation 4
In vitro data	Emitted dose (µcg)	70.9	73.9	76.7	88.1
	Fine particle dose (µcg)	25.6	17.2	20.5	26.0
In vivo data	30 minute urinary excretion (% dose)	2.7%	1.7%	1.8%	2.7%
	24 hour urinary excretion (% dose)	28.5%	18.5%	17.1%	27.2%
p<0.05 (formulations 1 & 4 versus formulations 2 & 3) for urinary excretion					

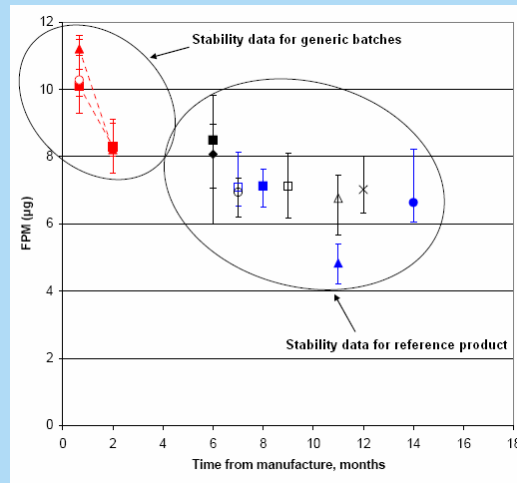
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Why is demonstration of BE on PK difficult?

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Change of FPM with Time at 25 °C: Generic Fluticasone Propionate DPI vs Reference Product



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Variability in reference and test product FPM

How could this be addressed?

- Characterise rates of FPM 'decay' for both T and R
- Assuming similar rates of decay, compare T and R batches of similar age in PK study
- Since age of available R product unpredictable manufacture several T batches to facilitate a valid PK study comparison
- Consider PK study which includes ≥ 2 R periods using batches of different ages / FPMs (non-extreme)
 - Should regulators scale acceptance limits for T/R on basis of R/R comparison? Would be scientifically valid

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Incomplete charcoal blockade

Charcoal blockade may be incomplete

- Budesonide effectively (96%) adsorbed by 40 gm charcoal¹
- Sodium cromoglicate (SCG) effectively (100%) adsorbed by 25 gm charcoal (but not by 10 gm)²
- Terbutaline effectively (97%) adsorbed by 30 gm charcoal (but not by 15 gm)³
- Validation of charcoal block not routinely submitted to date, or requested, for other orally bioavailable actives for which published data may be lacking
- Efficacy of charcoal blockade should be confirmed for each orally available active substance if not known, to assure results can be interpreted

1. Lathema, Br J Clin Pharm 2004
2. Assefian, Br J Clin Pharm 1999
3. Borgstrom, Univ Uppsala 1993

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Incomplete charcoal blockade

Does incomplete blockade have important ramifications?

- Hypothetical charcoal block study where blockade incomplete:
 - Give 100 µcg drug dose
 - MDI delivers 10% dose to lungs, 90% to GIT
 - Pulmonary bioavailability is 100%, oral BA depends on active
 - Assume charcoal block is only 96% effective
 - If oral BA 40% (e.g., BDP), of estimated 'pulmonary' dose
 - 10 µcg is absorbed via lungs
 - 1.4 µcg is absorbed via GIT
(90 µcg x 40% BA x 4% not adsorbed by charcoal)
 - i.e. 87% of estimated 'pulmonary' dose is absorbed via lungs
 - If oral BA 10% (e.g., budesonide, terbutaline)
 - 97% of estimated 'pulmonary' dose is absorbed via lungs

1. Lahtela, Br J Clin Pharm 2004
2. Aswaria, Br J Clin Pharm 1999
3. Borgstrom, Univ Uppsala 1993

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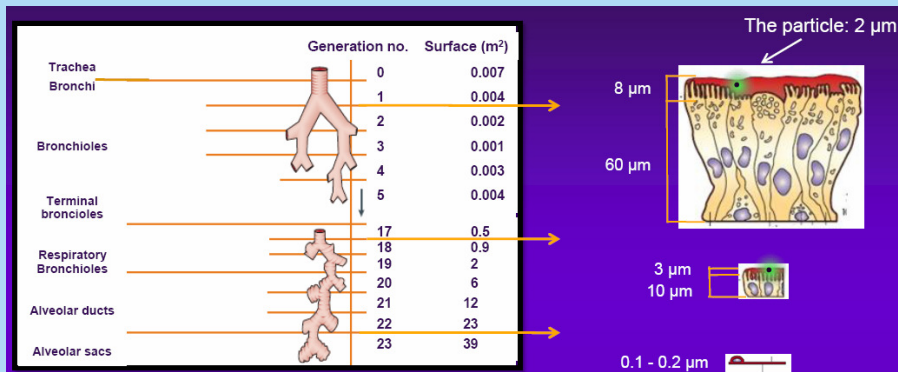
Incomplete charcoal blockade

- However, even in worst case, i.e., BDP:
 - If differences exist in pulmonary vs GI deposition for T vs. R, will be reflected in PK profiles (different absorption rates via lungs / GIT)
 - i.e., BE very unlikely in this scenario
- Summary:
 - Efficiency of charcoal blockade regimen should be validated as part of MAA where published data lacking
 - Nonetheless differential pulmonary versus GI drug absorption rates mitigate confounding influence of incomplete block

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Can PK discern regional deposition differences?



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Can PK discern regional deposition differences?

- Recently proposed that PK may evidence differences in regional deposition for less soluble OIPs¹

PK simulation of effect of dissolution rate and regional deposition on AUC

Dissolution t _{1/2} (min)	AUC (ng.h/mL)		
	Central Deposition (%)		
	25	50	75
540	1.52	2.04	2.55
360	1.80	2.27	2.74
240	2.06	2.47	2.87
120	2.49	2.76	3.02
60	2.82	2.98	3.14

V.interesting although note assumptions

Dose=200μg, CL=60L/h, Vd=300L, oral BA=0%, dissolution t_{1/2} twice as high in peripheral lung

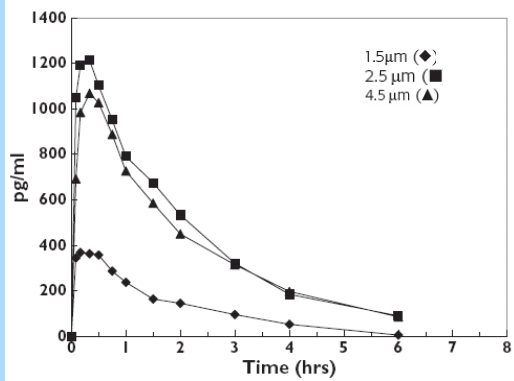
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1. Goyal & Hochhaus, Resp Drug Deliv 2010

Can PK discern regional deposition differences?

Esposito-Festen, Br J Clin Pharm 2007

- 3-way crossover trial
- 3 monodisperse aerosols (1.5, 2.5, 4.5 µm MMAD)
- Charcoal block



- Deposition with 1.5 µm aerosol significantly ↓ vs. other particle sizes
- 2.5 & 4.5 µm aerosols not significantly different
- Unfortunately no scintigraphic data
- Not confounded by differences in FPD, formulation etc

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Can PK discern regional deposition differences?

- Also suggested that PK may lack sensitivity to evidence differences in regional deposition for highly soluble OIPs¹

PK simulation of effect of absorption rate and regional deposition on C_{max} (absorption is rate limiting)

Absorption t _{1/2} (min)	C _{max} (ng.h/mL)		
	Central Deposition (%)		
	25	50	75
30	0.51	0.49	0.46
20	0.55	0.52	0.50
10	0.59	0.57	0.56
5	0.62	0.61	0.60

- Raises questions re sensitivity of C_{max} to discern regional differences in distribution proposed by some authors re SCG
- Note Usmani's study - ~11% difference in salbutamol central deposition associated with relevant differences in effect

1. Goyal & Hochhaus, Resp Drug Deliv 2010

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Can PK discern regional deposition differences?

Summary:

- Possibly. Evidence not particularly compelling to date
- Pulmonary drug absorption complicated – correlated with lipophilicity / polarity
- Lack of regional absorption rate data for (different) OIPs
- Difficult to extrapolate limited published data to all OIPs, or to accept simulations without further *in vivo* validation
- Further studies, on spectrum of OIPs, incorporating **both** PK and scintigraphy required to definitively confirm/refute
 - If monodisperse aerosols used, ideally compare aerosols with reasonably similar characteristics to be more reflective of commercial T/R context
- However, plausible that T product with similar *in vitro* characteristics to R, and BE on PK, could exhibit important differences in regional distribution?

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Paediatrics

- Some debate
- For novel OIP irrefutable that safety / efficacy should be evaluated in children
- For a generic, OIP guideline states:
 - *In children pulmonary deposition studies are **not appropriate** [to determine **efficacy**]. PK studies as a surrogate for efficacy **only imply efficacy**... and have **insufficient advantages** over pharmacodynamic and/or clinical studies in ...children to warrant their use*
 - *In children **safety** data **cannot be extrapolated** from adults with asthma or from a surrogate adult population*
 - *[Unless] **in vitro** criteria for equivalence .. all .. fulfilled, clinical development .. in children.. required*
- Thus far regulatory practice in line with above. Rational?

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Paediatrics

- In children pros/cons of PK vs. PD essentially same as in adults.
- Hence PK for efficacy in children should be as scientifically valid
- Is extrapolation (for efficacy and safety) from adults valid?
 - Although airways geometry in adults vs. children varies, can 2 products which are equivalent in adults be inequivalent in children?
 - If T & R are pMDIs, unlikely (although both with / without spacer comparisons required)

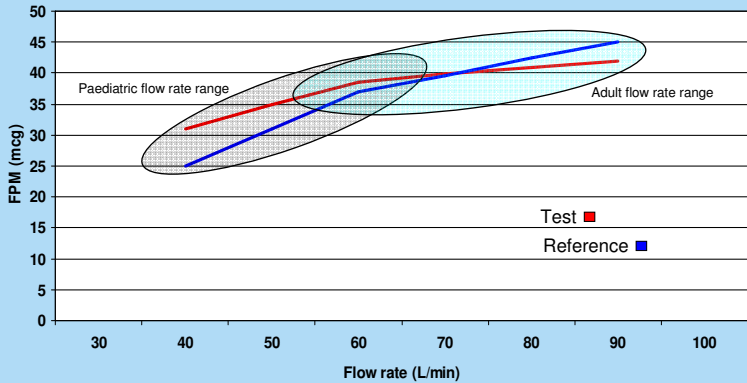
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Paediatrics

- Where relative delivery from two DPIs varies across the pressure drop/flow rate range, adult equivalence may not reflect paediatric comparison
- Paediatric data important

Example 1: T/R DPI differences across flow rates



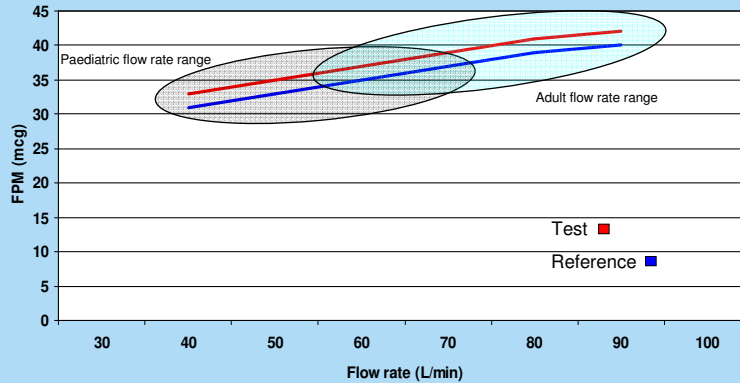
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Paediatrics

- Where relative delivery from two DPIs does not vary across the pressure drop/flow rate range, extrapolation from adults likely to be valid (assuming no handling issues)

Example 2: T/R DPI differences across flow rates



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PK allows targeted clinical development

- Clearly difficult to achieve BE on PK
- Significant benefit is that it allows targeted development / assessment
 - If T exhibits greater pulmonary deposition vs. R, efficacy concerns appear unlikely
 - If T exhibits lesser pulmonary deposition vs. R, PD evidence of equivalent efficacy important
 - If T exhibits lesser systemic deposition vs. R, safety concerns appear unlikely
 - If T exhibits greater systemic deposition vs. R, PD evidence of equivalent safety important
 - Personal experience: T/R PK differences regularly reflected in lesser PD signal

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PD studies

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- Few PD equivalence studies as yet through the regulatory process
- Reproducibility of published PD efficacy models in registration studies remains to be seen:
 - Bronchodilatation
 - PC20
 - eNO
 - Asthma stability
- Surprisingly few companies have proposed screening for DR. Why?
 - Will ↑ assay sensitivity, ↓ sample size
- Given relative dearth of consistent data, pilot studies prudent

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PD studies

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- Conversely published PD safety models appear to be reliably reproducible in registration studies:
 - for β -agonists - metabolic/physiological endpoints
 - For ICS - 24-hr plasma cortisol (not UFC), knemometry
- ? for muscarinic antagonists

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PD safety studies

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- Principals of sensitive efficacy study design as described in OIP guideline fairly standard
- Same principles (chiefly for assay sensitivity) should apply to safety studies
- Areas of potential debate / uncertainty:
 - Paediatrics
 - Dose levels (for safety)
 - Study duration
 - Equivalence limits for safety parameters

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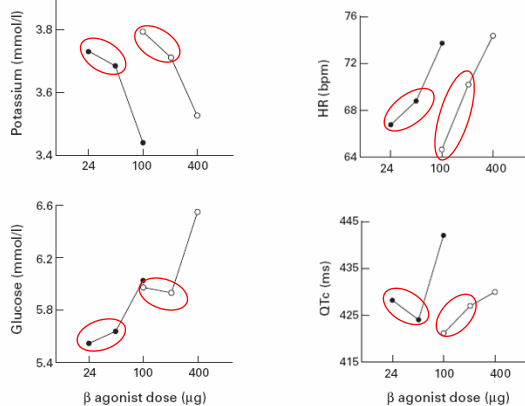
Dose levels in safety studies

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Dose level

- OIP guideline: *pharmacodynamic ... safety profile must ... be investigated following administration of the **maximum recommended dose***
- Optimal approach?

Dose-response curves for formoterol (●) and salmeterol (○) using mean maximum values over 4 hrs post-dose (Guhan, Thorax 2000)



- In a bioequivalence setting, assay sensitivity of critical importance

- Parallels with clinical context (e.g., usual clinical dose) secondary

- Analogous to FDA levothyroxine guidance (600 µcg BE study)

- Similar approach should be applied to study duration – i.e., determined by assay sensitivity, not relevance to clinical setting

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Dose levels in safety studies

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- Assessment of suprathreshold doses clinically relevant?
- Serious ADRs, e.g., adrenal crisis, arrhythmia rare
- In most patients modest differences in dose delivery between devices probably unimportant
- However, differences may be relevant in outliers
 - Patients on multiple concomitant medications / severe coexisting disease frequently excluded from trials
 - Patients with difficult disease who may be subjected to above-approved doses
- Demonstration of equivalence with sensitive assay (with suprathreshold doses if necessary) should provide assurance without recourse to large-scale trials in 'outliers'
- ? Approach for muscarinic antagonists

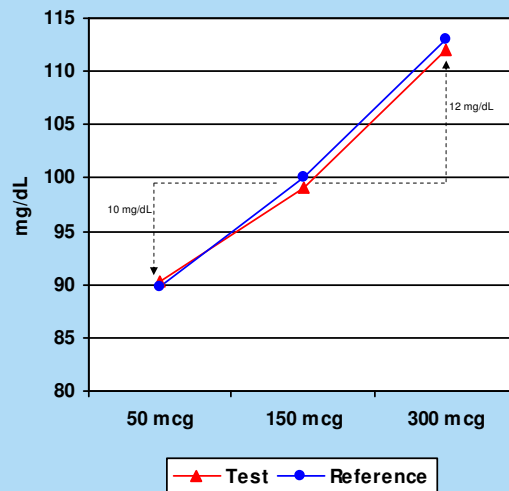
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Safety studies – equivalence margins

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Blood glucose at 30 mins post-salmeterol dose



Defining acceptable equivalence margins

- Dose-response
- Margins should exclude overlap with higher/lower doses
- What are differences between doses?
 - R150 minus R50 ~10 mg/dL
 - R300 minus R150 ~12 mg/dL
- What is the difference between T & R at a given dose?
 - T minus R @ 150 mcg = 0.5 mg/dL (95% CIs -5.1,6.1)
- Define limits *a priori*
- If fail to do so or pre-specified margins excessive, observed data still allows consideration of equivalence

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Conclusion

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- OIP guideline major step forward for EU development
- Some issues require further consideration
- Algorithm generally rational
- V.tight limits on *in vitro* data given limited IVIVC appropriate
- Balance between reliance on PK/PD data more debatable. OIP guideline 2009:..
equivalent pulmonary deposition demonstrated through PK ... might be ... sufficient.
However, in general, therapeutic equivalence must be demonstrated by means of
appropriate pharmacodynamic and/or clinical studies
- Main reason for the above could be considered to be difficulty of demonstrating BE on PK - not concerns as to relevance of PK
- Further PD data will be of great interest
 - Generally likely to support PK-PD correlation previously reported
 - Reproducibility /feasibility of a number of models to be ascertained

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Thank you

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