PK/PD Modeling and Simulation for Efficacy and Safety of Corticosteroids in Asthma and Inflammation

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University of Florida

THE BURRILL REPORT Lif

Business Finance Health Law/Policy Tech/Innovation

December 7, 2012

DRUG DEVELOPMENT

New Estimate of Drug Development Costs Pegs Total at $1.5 Billion

Office of Health Economics suggest more flexibility and better alignment needed between stakeholders and innovators is needed.

DANIEL S. LEVINE

The Burrill Report

The cost of drug development has been a matter of controversy, particularly because the high cost and long time to bring a drug from discovery to market is used to justify high prices for innovative drugs. Now a new report that examines a wide range of previous studies pegs the total at $1.5 billion.

"The R&D costs identified in our study are driven by a combination

FDA Critical Path Documents

Biomarker vs. Surrogate Endpoint

Biomarker

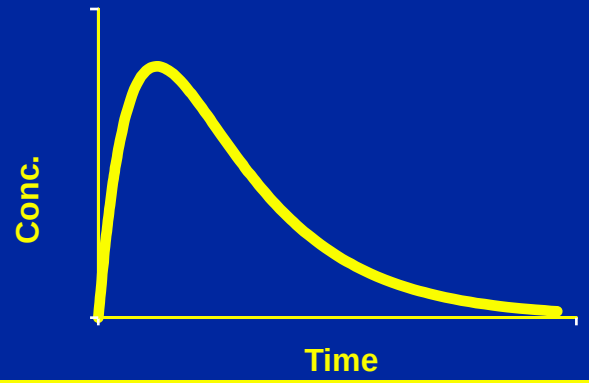
Drug- or disease-induced measurable change (physiological, pathophysiological, biochemical or other)

Surrogate Endpoint

Biomarker that has predictive value for therapeutic outcome

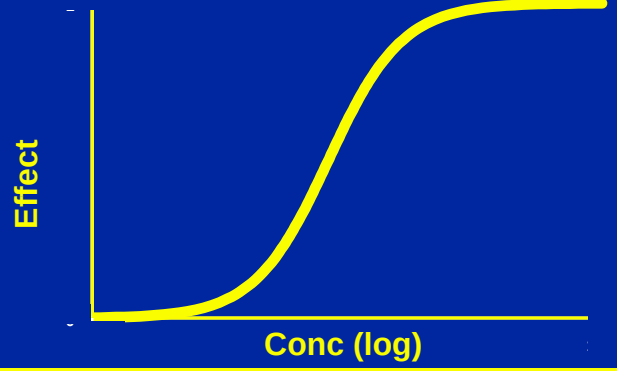
Pharmacokinetics

conc. vs time



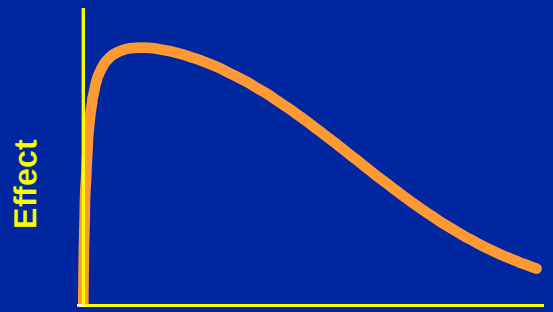
Pharmacodynamics

conc. vs effect

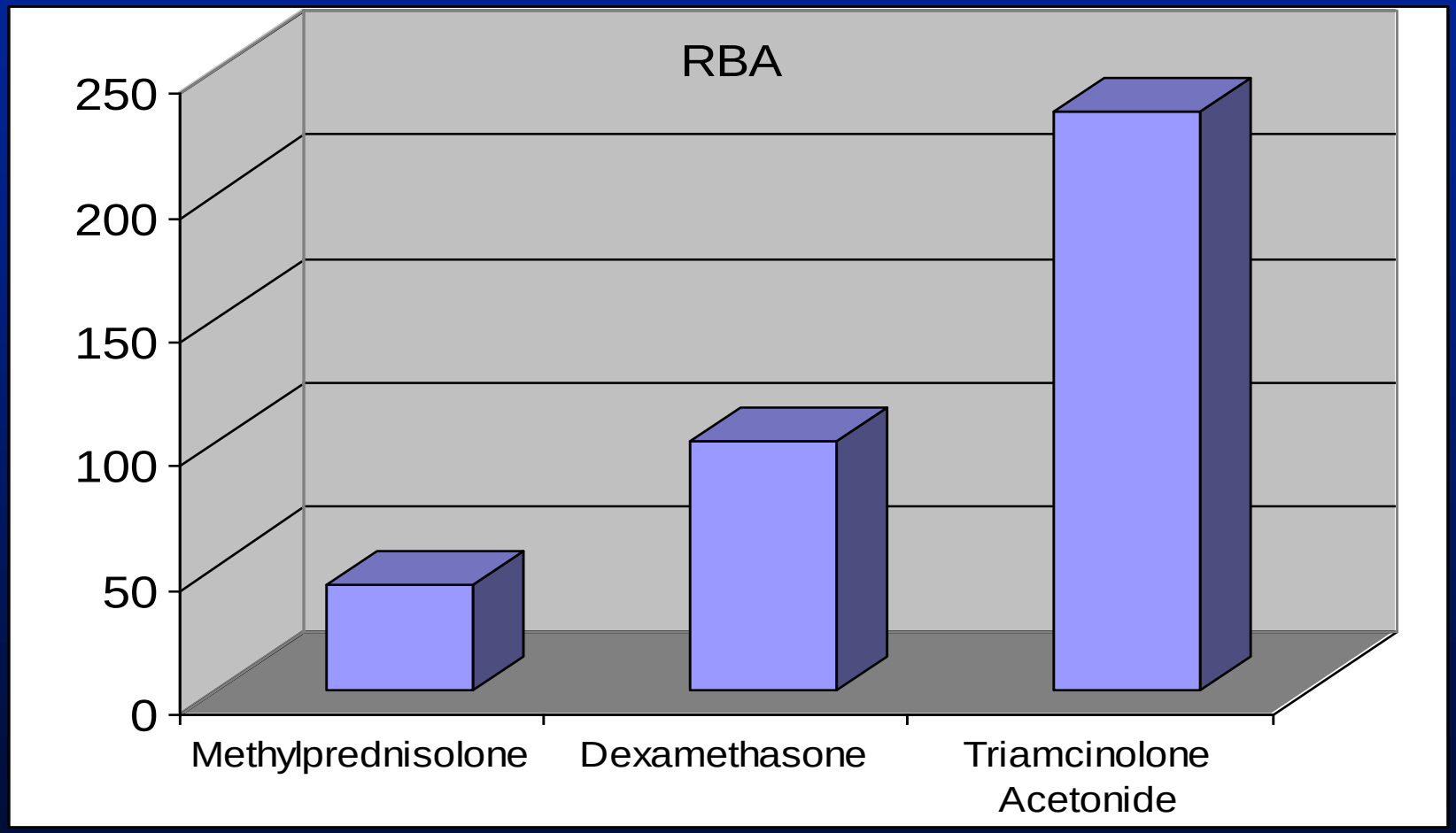


PK/PD

effect vs time

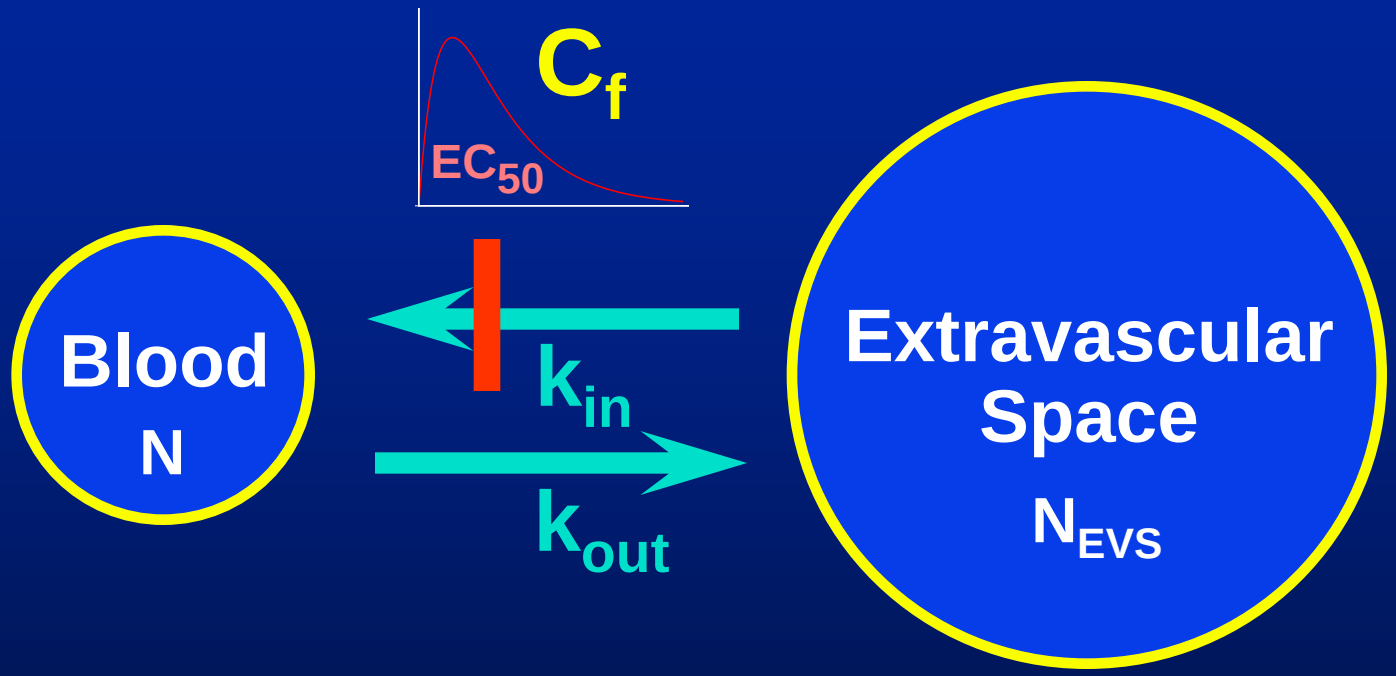


Pharmacodynamic Potency



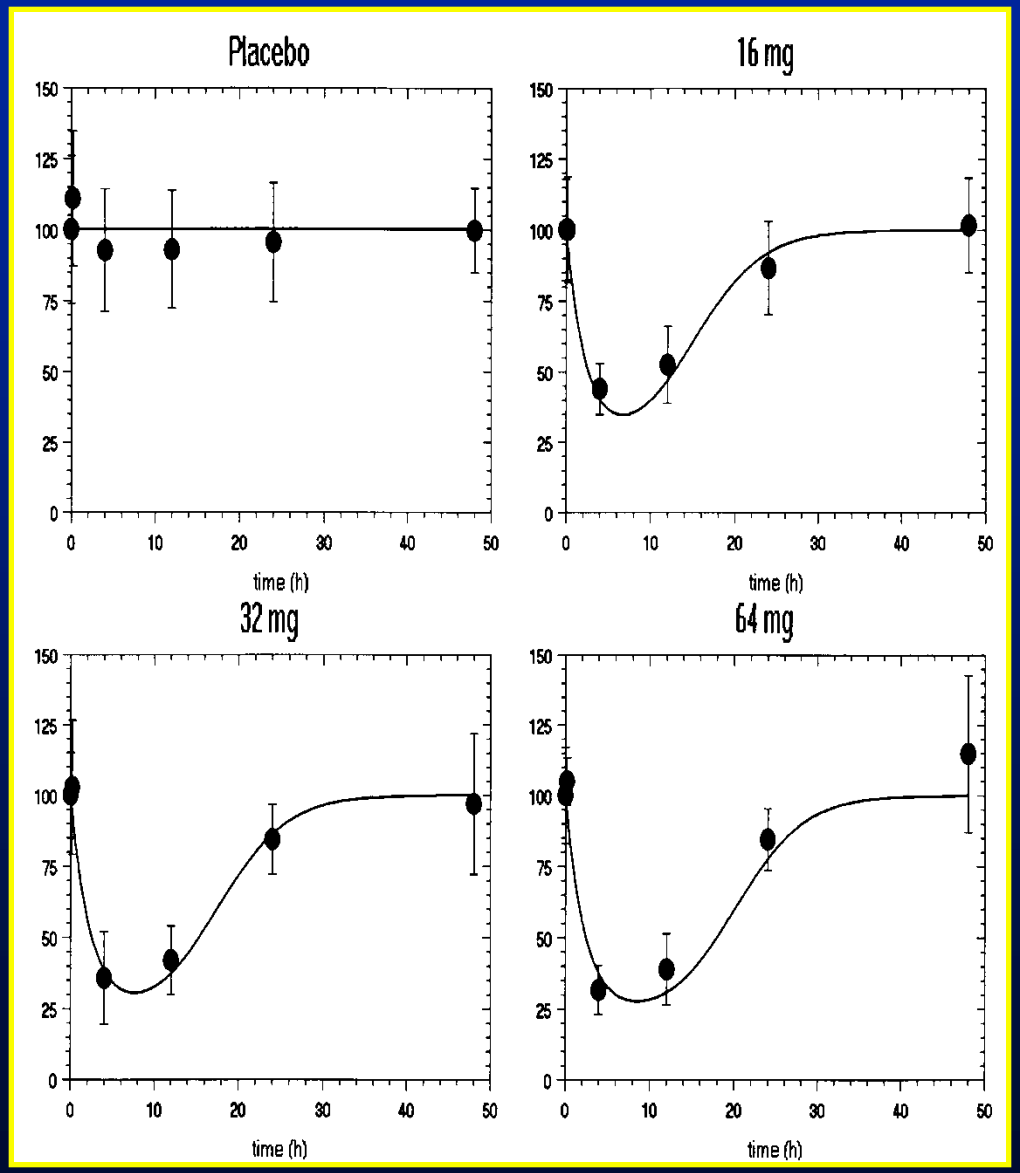
Lymphocyte Trafficking Model

$N << N_{EVS}$

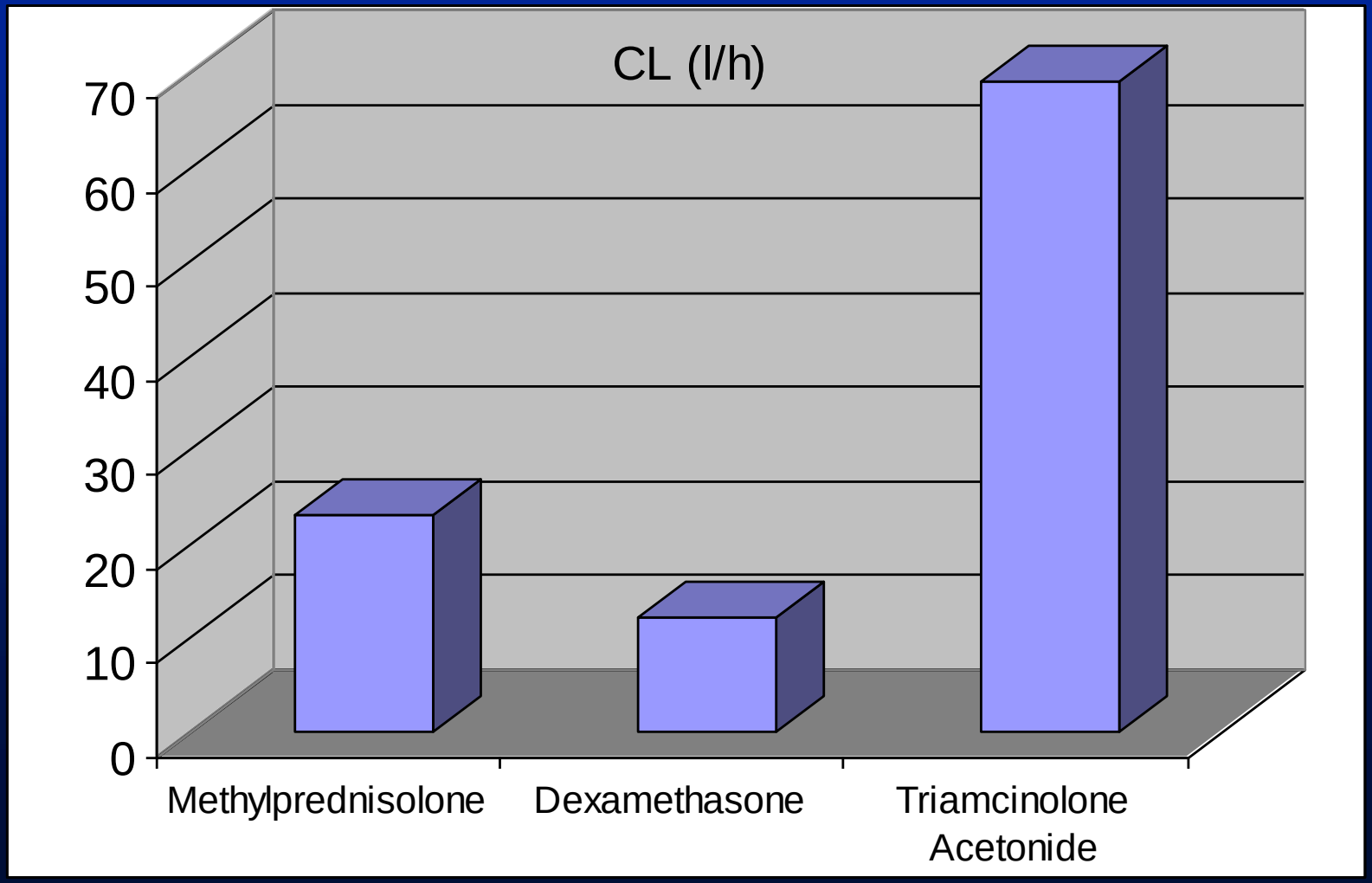


$$\frac{dN}{dt} = k_{in} \cdot \left(1 - \frac{E_{max} \cdot C_f}{EC_{50} + C_f} \right) - k_{out} \cdot N$$

Methylprednisolone and Lymphocytopenia

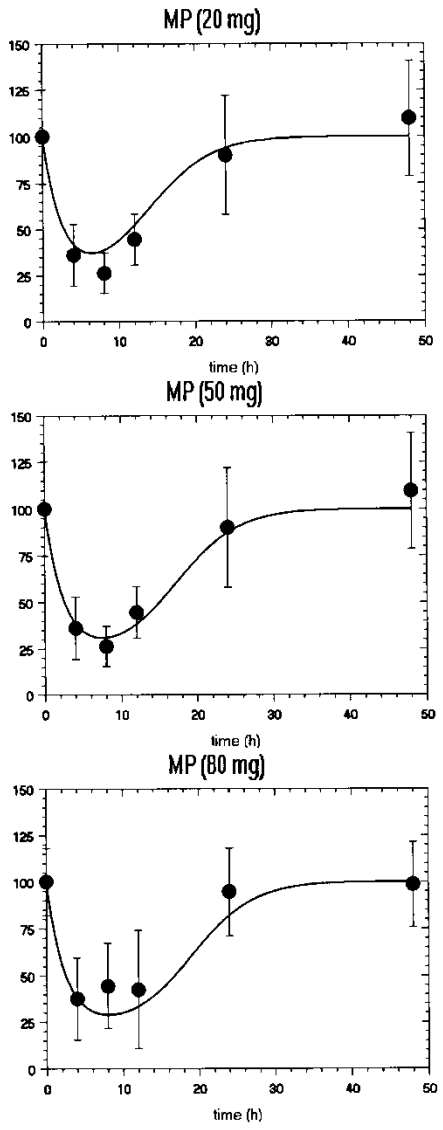


Pharmacokinetic Clearance

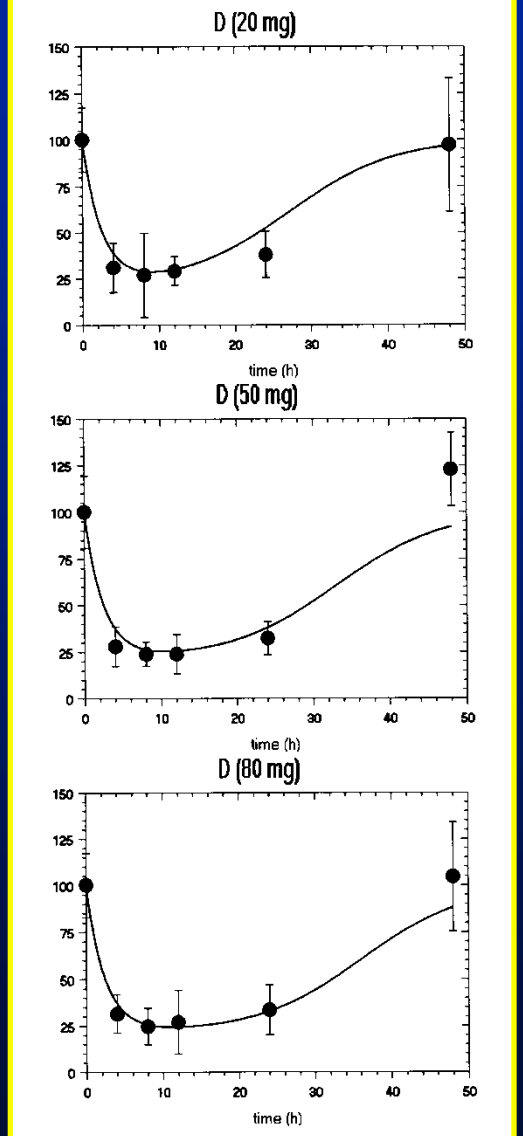


Lymphocytes

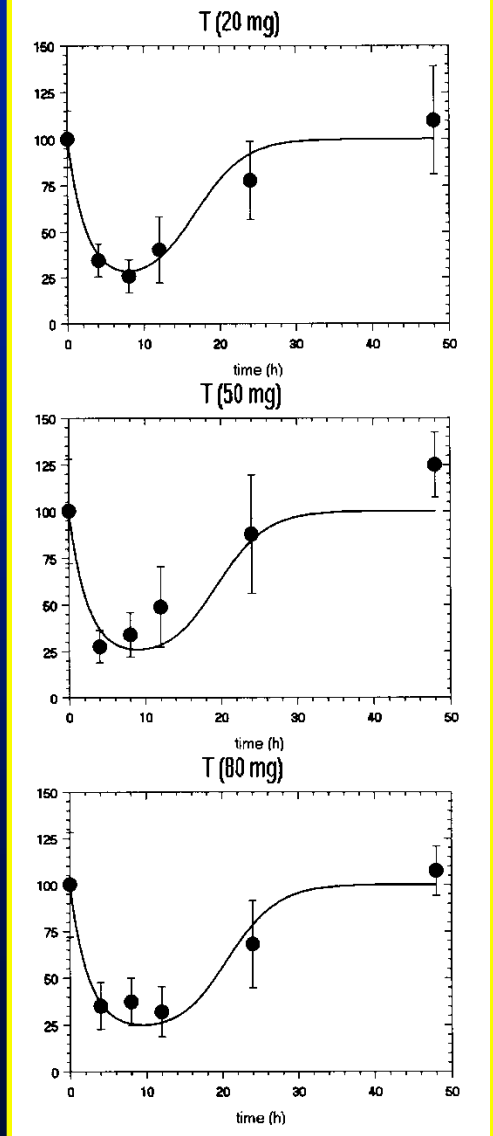
Methylprednisolone



Dexamethasone

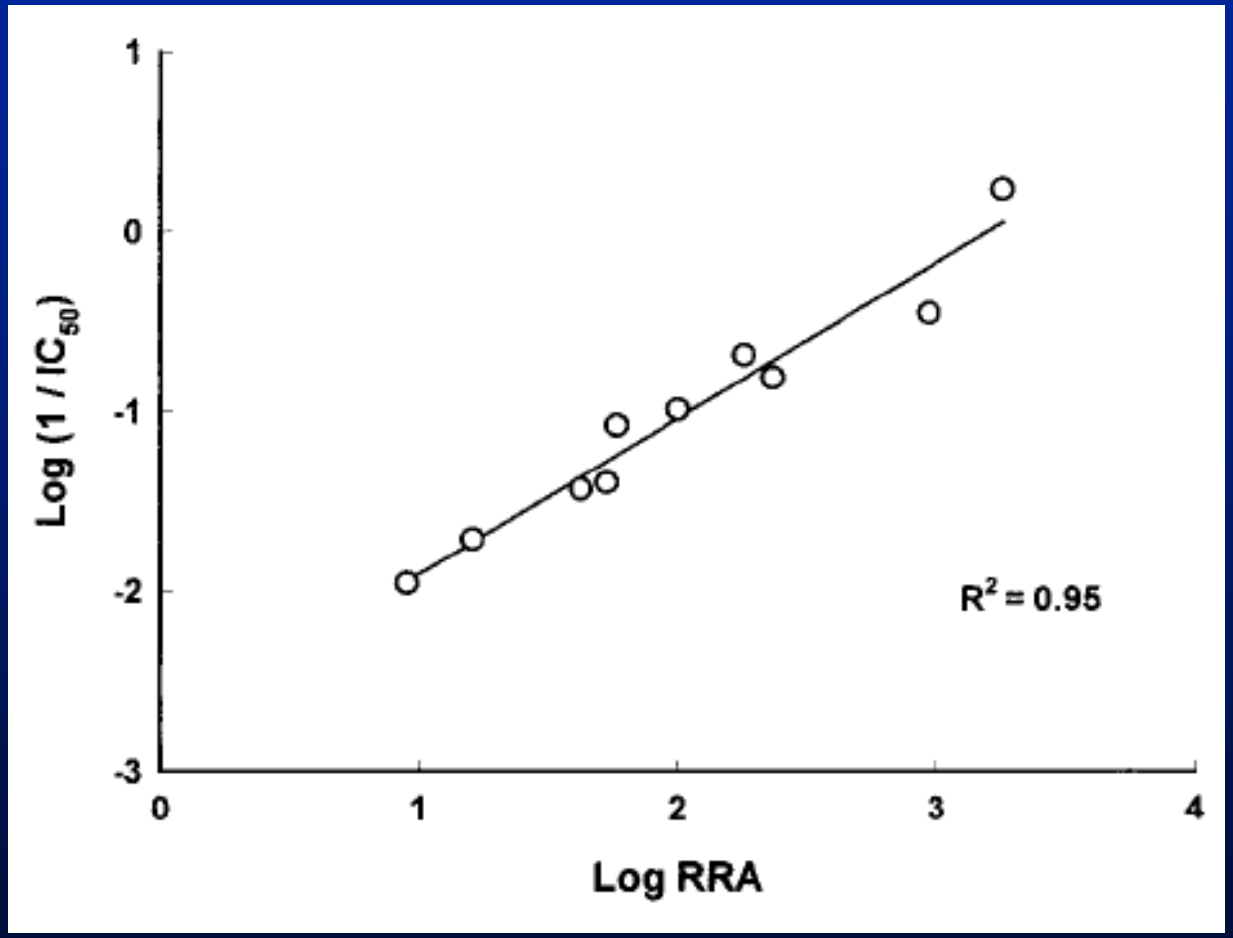


Triamcinolone Acetonide



Correlation $1/EC_{50}$ vs. Relative Receptor Binding

EC_{50} for modulation of lymphocytes



Mager et al. 2003

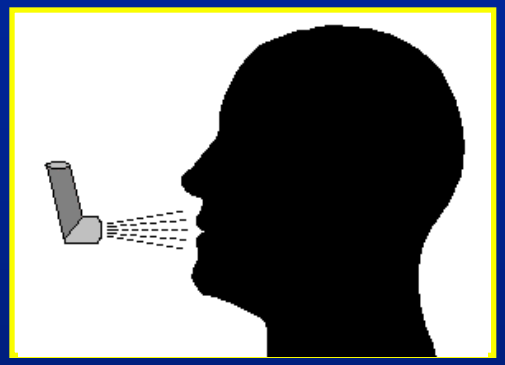
Systemic Equivalency Dose

$$DR_{50} = \frac{CL \cdot EC_{50}}{F \cdot f_u}$$

Pharmacodynamic vs. Therapeutic Potency

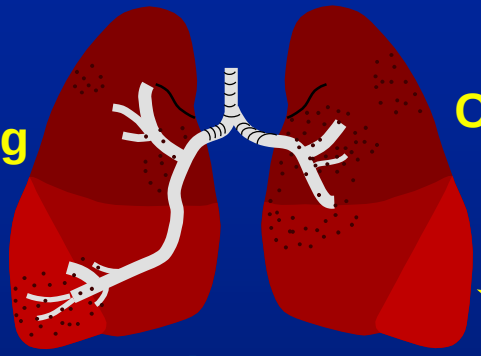
	RRB (DEX=100)	EC_{50} [ng/ml]	CL [l/h]	F [%]	f_u	DR_{50} [mg/day]	Rel.Pot. (HC=1)	Clin.Pot. (HC=1)
Betamethasone	55	2.7	12	72	0.36	3.1	21.9	25
Dexamethasone	100	1.7	16	83	0.32	2.4	28.6	25
Triamcinolone acetonide	233	0.8	37	23	0.29	10.6	6.3	6
Methylprednisolone	42	5.6	21	99	0.23	12.3	5.5	5
Prednisolone	16	13.4	14	81	0.25	22.3	3.0	4
Fluocortolone	82	6.3	30	84	0.10	52.0	1.3	5
Hydrocortisone	9	29.9	18	96	0.20	67.2	1.0	1
Cloprednole	41	7.7	17	*100*	0.17	18.5	3.6	
21-Desacetyldeflazacort	29	3.1	114	92	0.60	15.3	4.4	

The Fate of Inhaled Corticosteroids



Mouth and pharynx

10 - 60 %
Deposited in lung



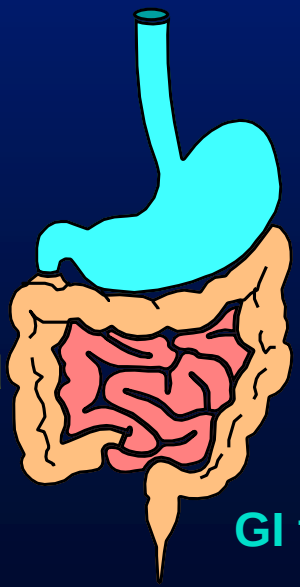
Lung

Complete absorption
from the lung

Systemic
Circulation

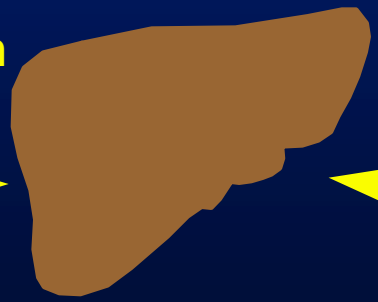
Orally bioavailable
fraction

40 - 90 % Swallowed
(reduced by spacer
or mouth rinsing)



GI tract

Absorption
from gut

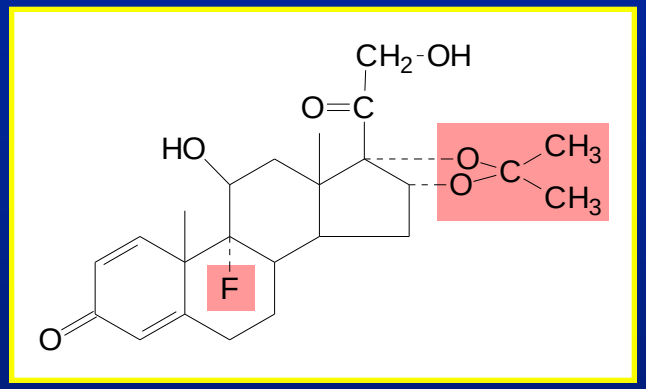


Liver

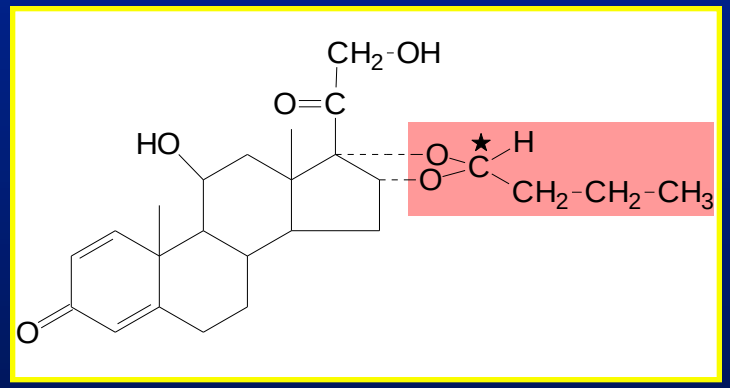
First-pass
inactivation

Systemic
side effects

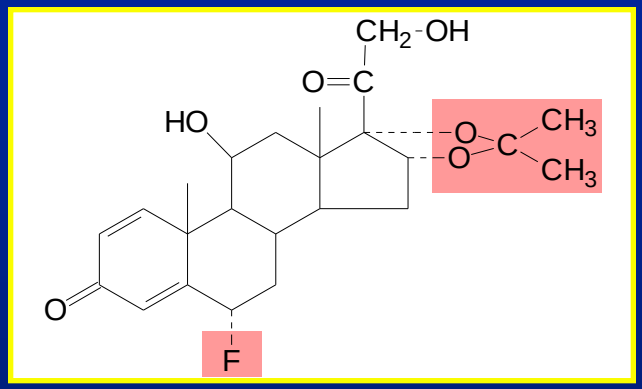
Corticosteroids for Inhalation



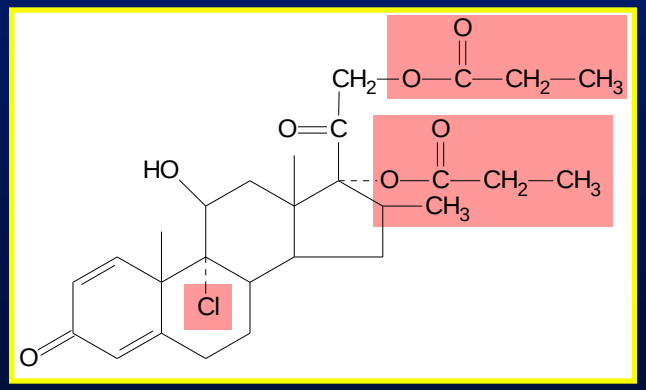
Triamcinolone acetonide



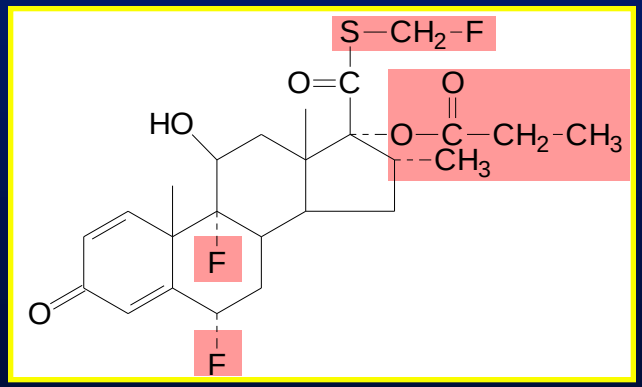
Budesonide



Flunisolide

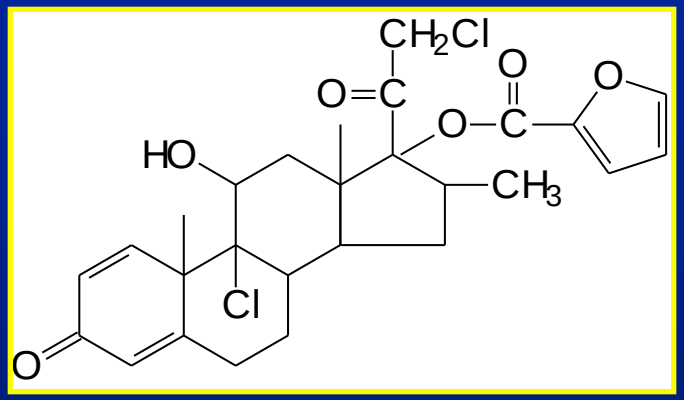


Beclomethasone dipropionate

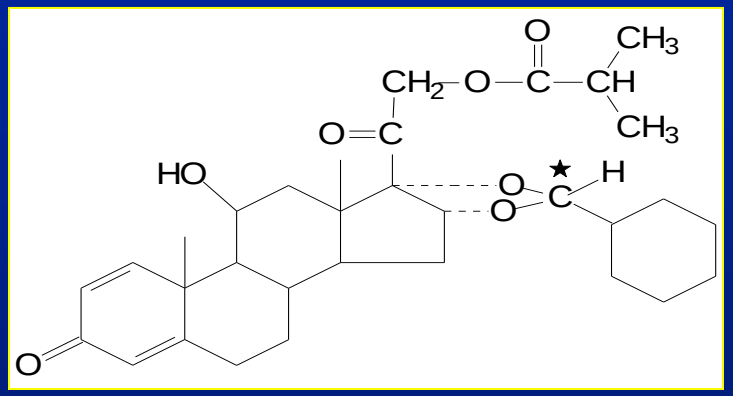


Fluticasone propionate

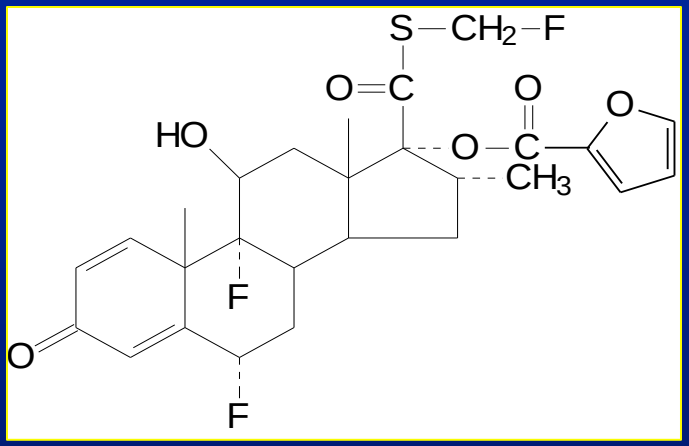
Corticosteroids for Inhalation



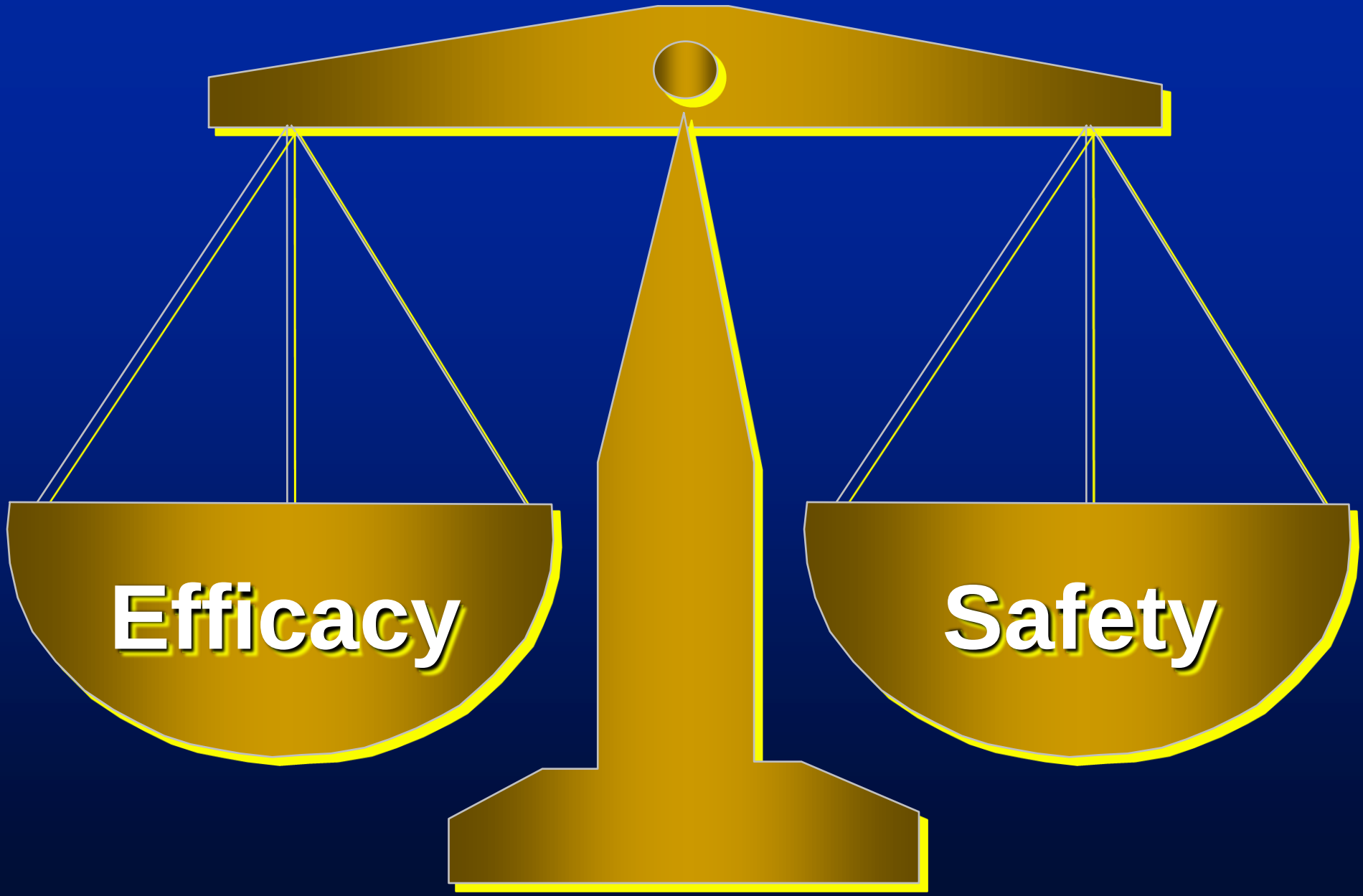
Mometasone Furoate



Ciclesonide



Fluticasone Furoate


Efficacy
Safety

Safety

Local Safety

- Linked to local exposure at site of administration

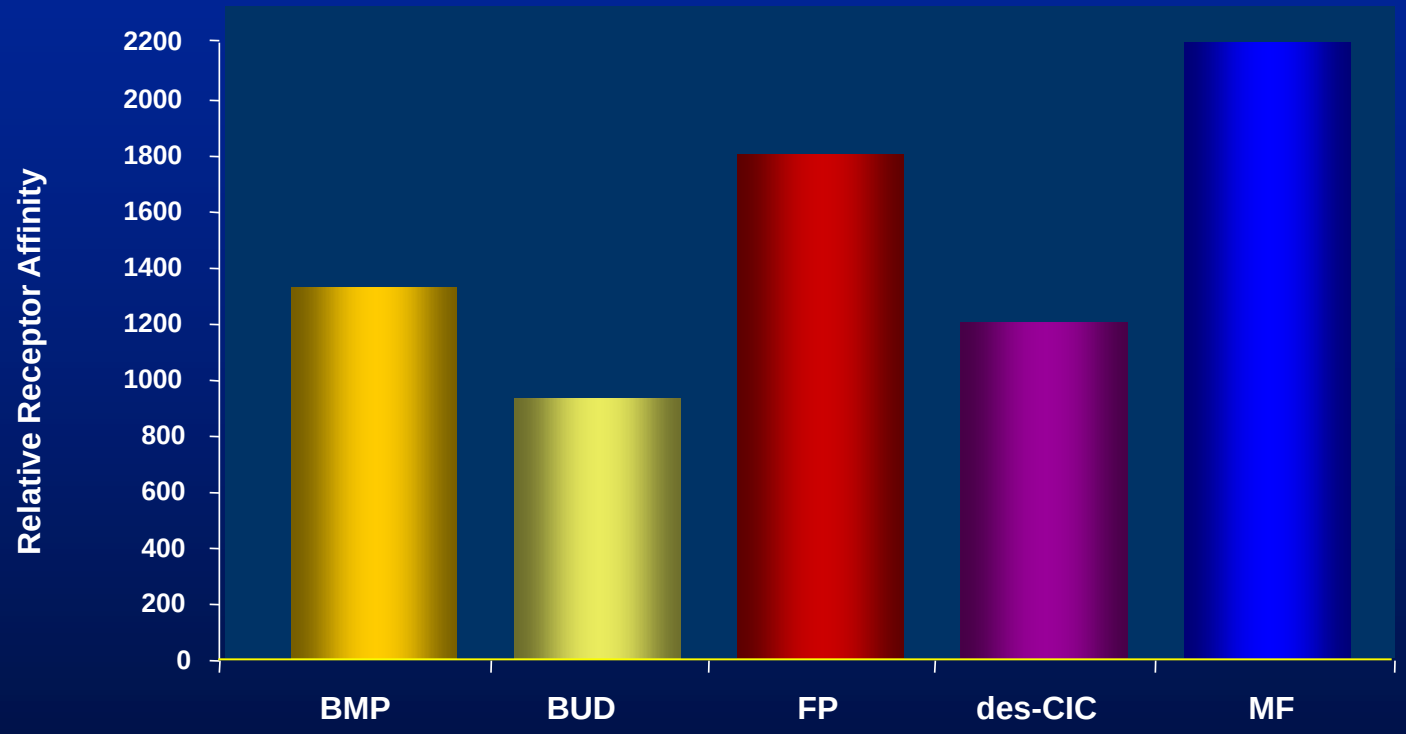
Systemic Safety

- Linked to systemic exposure (PK)
- Cortisol suppression serves as ‘common currency’ to compare different steroids
- All other systemic steroid effects (bone, eye, skin, growth etc.) follow from systemic exposure

Receptor Binding

- All effects of corticosteroids are mediated through the same receptor types throughout the body
- A drug with high receptor affinity has both potential for significant efficacy as well as significant adverse effects

Receptor Binding (cont'd)



RRA=relative receptor binding affinity (relative to dexamethasone).

BMP=beclomethasone monopropionate; BUD=budesonide; FP=fluticasone propionate; des-CIC=ciclesonide-active principle; MF = mometasone furoate.

Derendorf H. *Respir Med.* 1997;91(suppl A):22-28; Rohatagi S. et al. *J Clin Pharmacol* 2003;43:365-378. Valotis A, Hogger P. *Respir Res*. 2005;5:7-12.

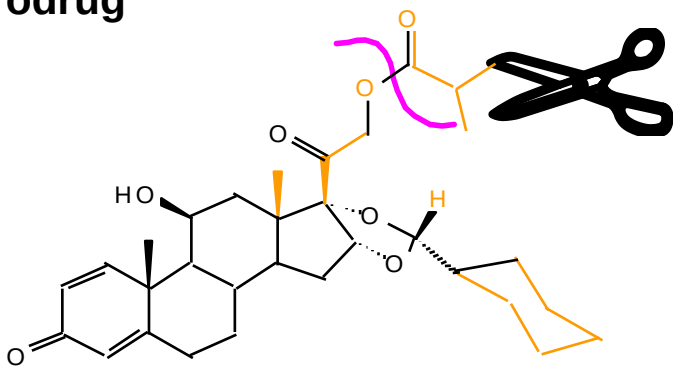
Pharmacokinetic Issues for Inhaled Corticosteroids

- Prodrug
- Bioavailability
- Clearance
- Half-life
- Protein binding
- Pulmonary residence time
- Lipid conjugation

Pro-Drugs and Local Safety

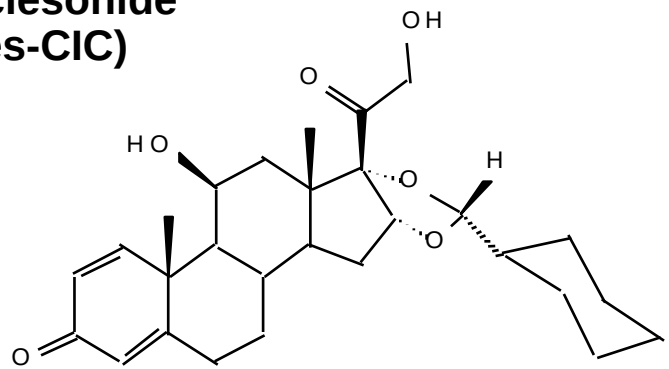
Bioactivation of ciclesonide

Ciclesonide Prodrug



Endogenous Activation by Airway Esterases

Activated Ciclesonide (des-CIC)



Receptor binding

12

des-CIC: desisobutyryl-ciclesonide

1200

Dietzel K, et al. *Prog Respir Res.* 2001;31:91–93.

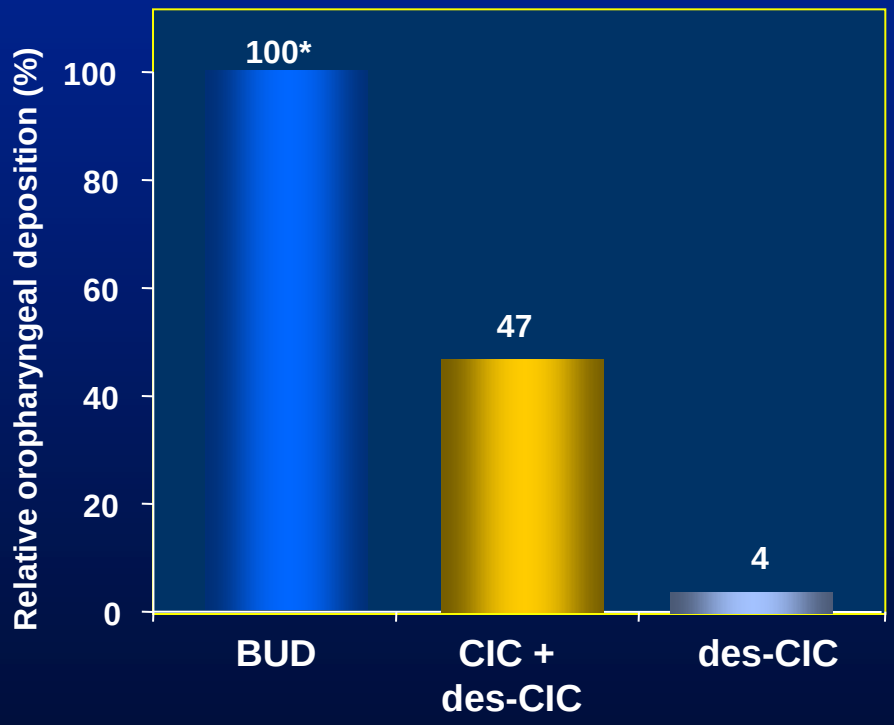
In Hansel TT, Barnes PJ, eds. *New Drug for Asthma, Allergy and COPD*. Basel, Karger.

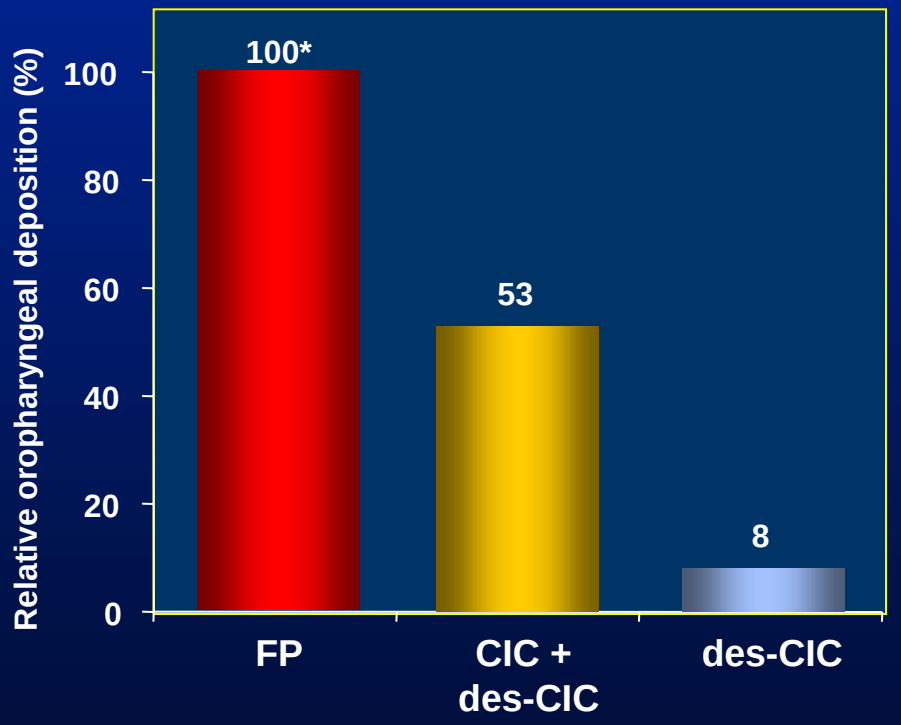
Advantages of On-site Activation

- Activation in the lung
- Minimized oropharyngeal side effects

Oropharyngeal Deposition/Activation

Ciclesonide (CIC) – low deposition and minimal activation to des-CIC in the oropharynx



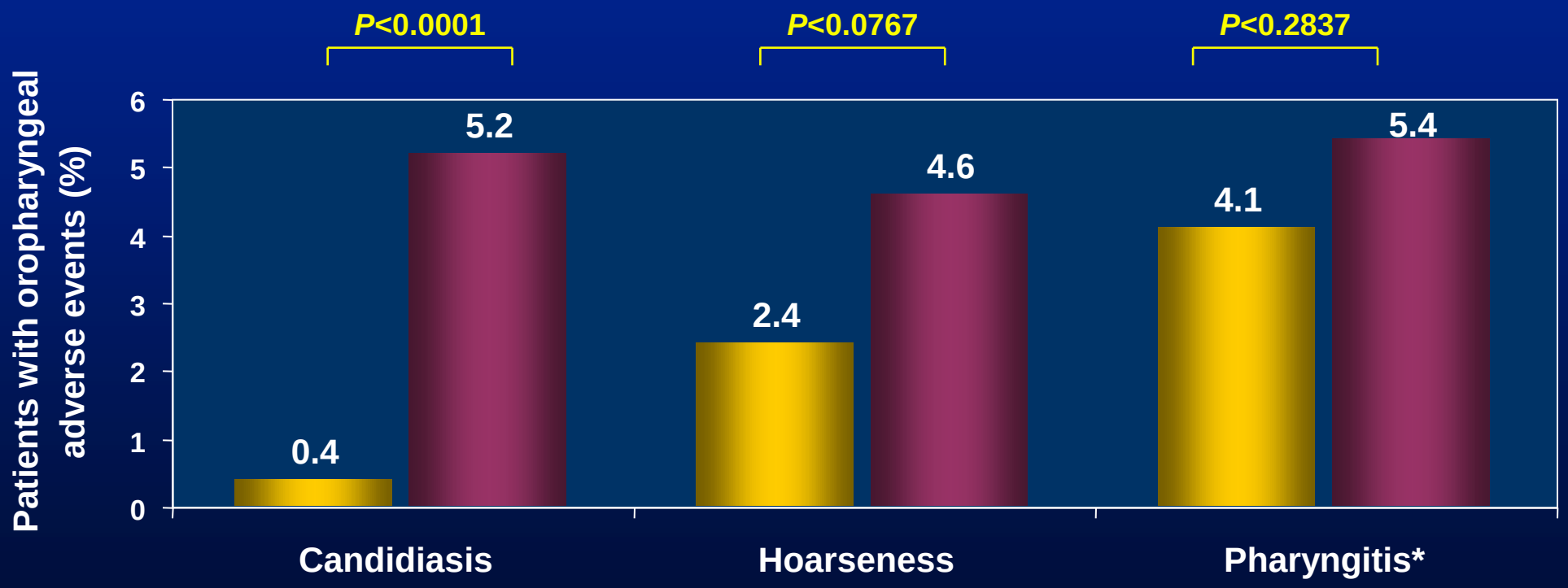


* The deposition values of budesonide (BUD) and fluticasone propionate (FP) were used as references adjusted for the molar dose (100%)

Nave R, et al. *Eur J Clin Pharmacol.* 2005;361:203-208.
Richter K, et al. *J Clin Pharmacol*. 2005;45:146-152.

Incidence of Oropharyngeal AEs in Asthma Patients Treated With CIC vs. FP

Proportion of patients with oropharyngeal adverse events: **Pooled analysis**



* Placebo: 4.4

Poster ATS2004, R Engelstätter, D Banerji, VW Steinijans, W Wurst

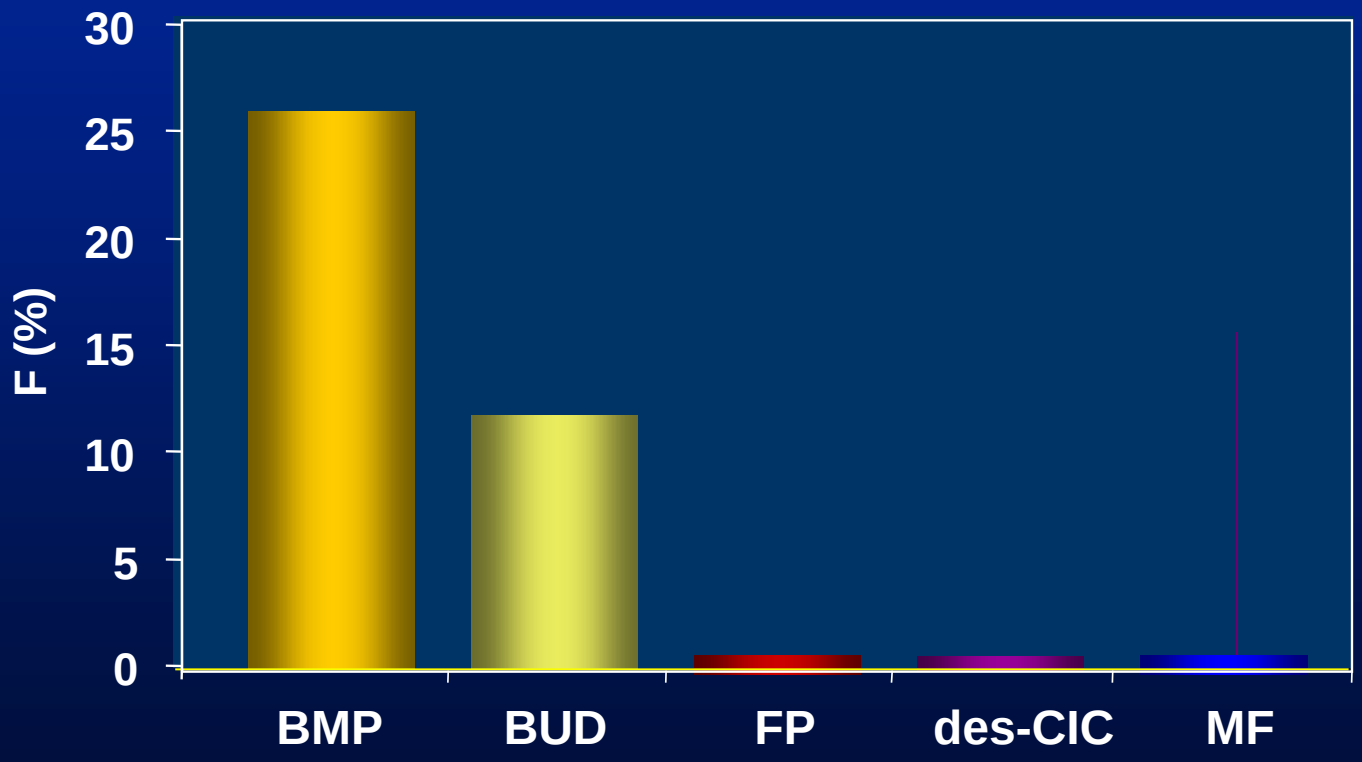
Bioavailability

Pulmonary Bioavailability +

Oral Bioavailability =

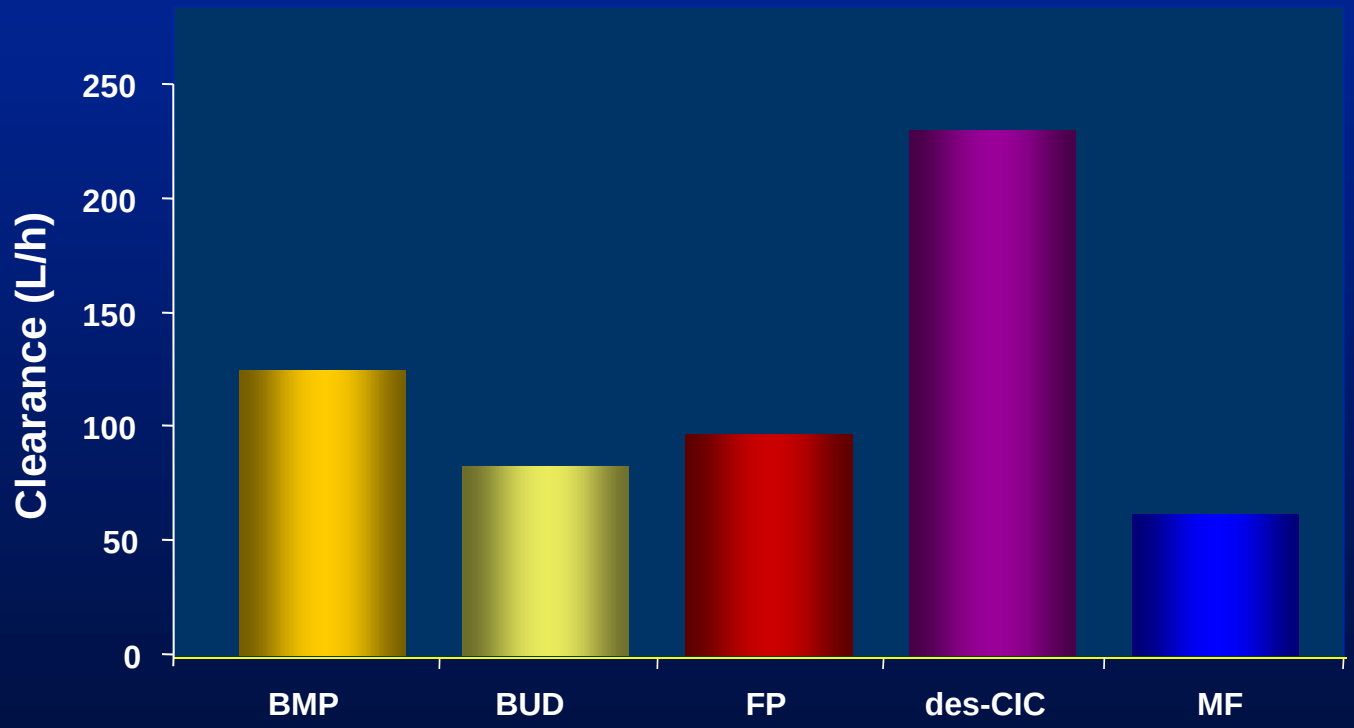
Systemic Bioavailability

Oral Bioavailability



Daley-Yates PT, et al. *Br J Clin Pharmacol.* 2001;51:400-409.
Derendorf H. *Respir Med.* 1997;91(suppl A):22-28.
ASMANEX TWISTHALER. Product Insert. 2003.

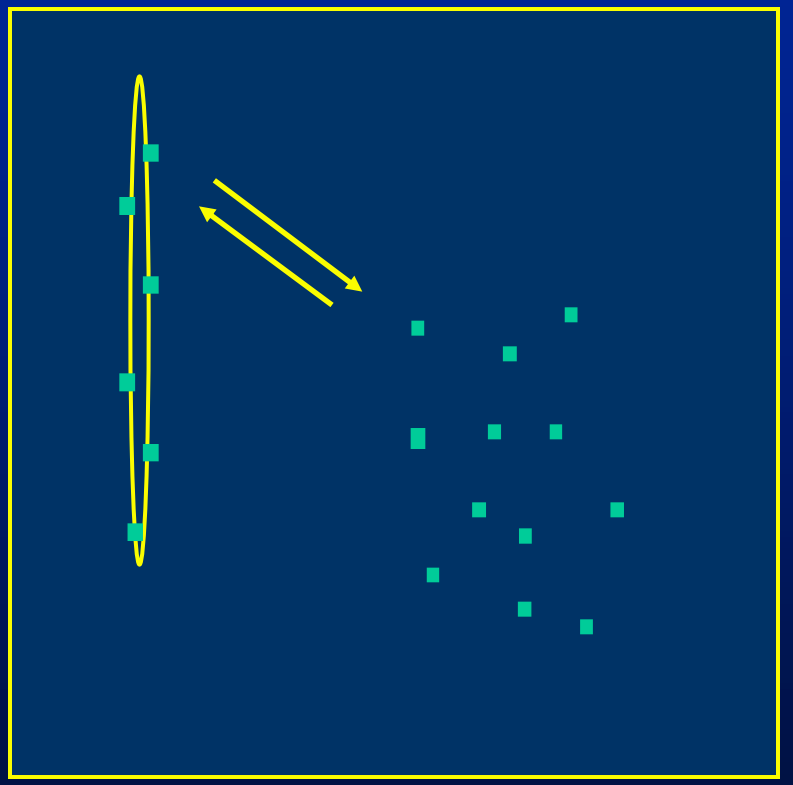
Clearance



Daley-Yates PT, et al. *Br J Clin Pharmacol.* 2001;51:400-409; Derendorf H. *Respir Med.* 1997;91(suppl A):22-28; Rohatagi S, Poster presented at the Thomas L. Petty Lung Conference, Aspen, 2002. Sharpe M, Jarvis B. *Drugs.* 2001;61: 1325-1350.

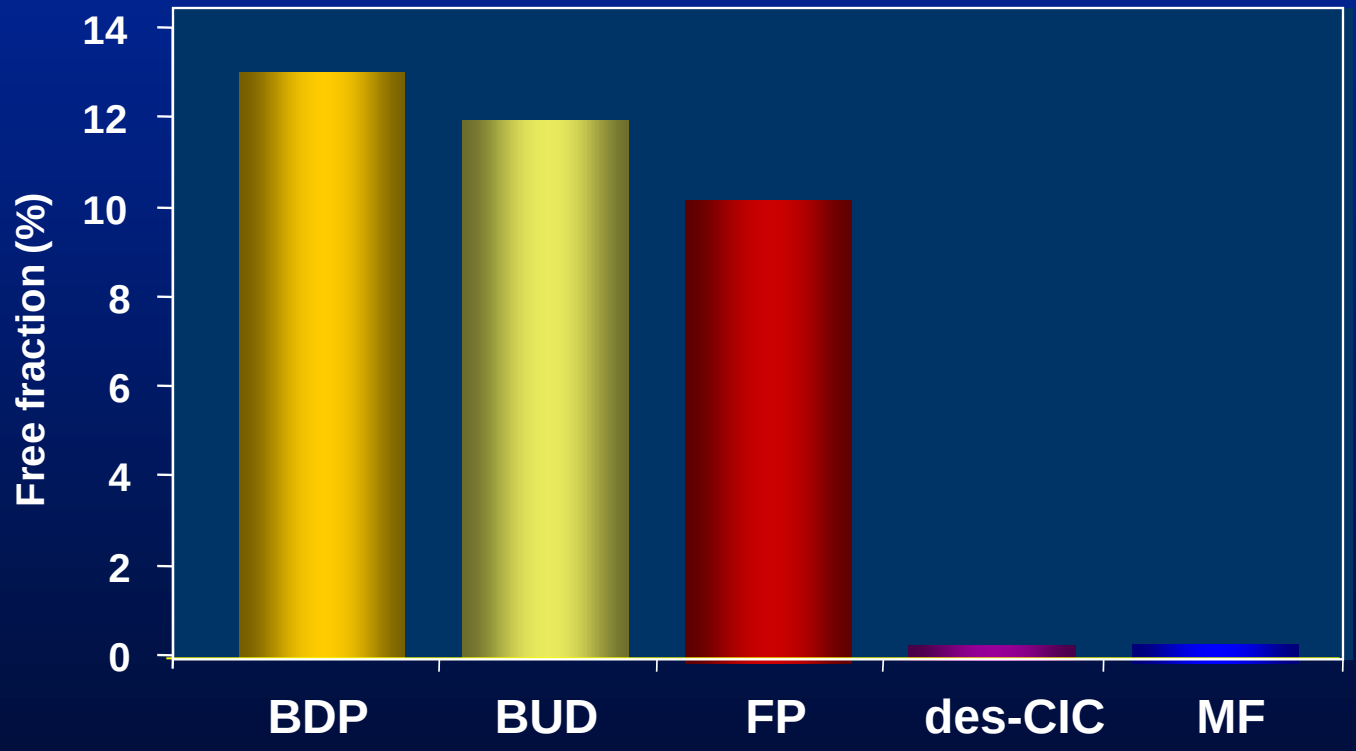
Plasma Protein Binding

- Reversible vs irreversible
- Linear vs nonlinear
- Rapid equilibrium
- Only the free (unbound) fraction of the drug at the receptor site is available for pharmacologic activity



Plasma Protein Binding (cont'd)

Free Fraction



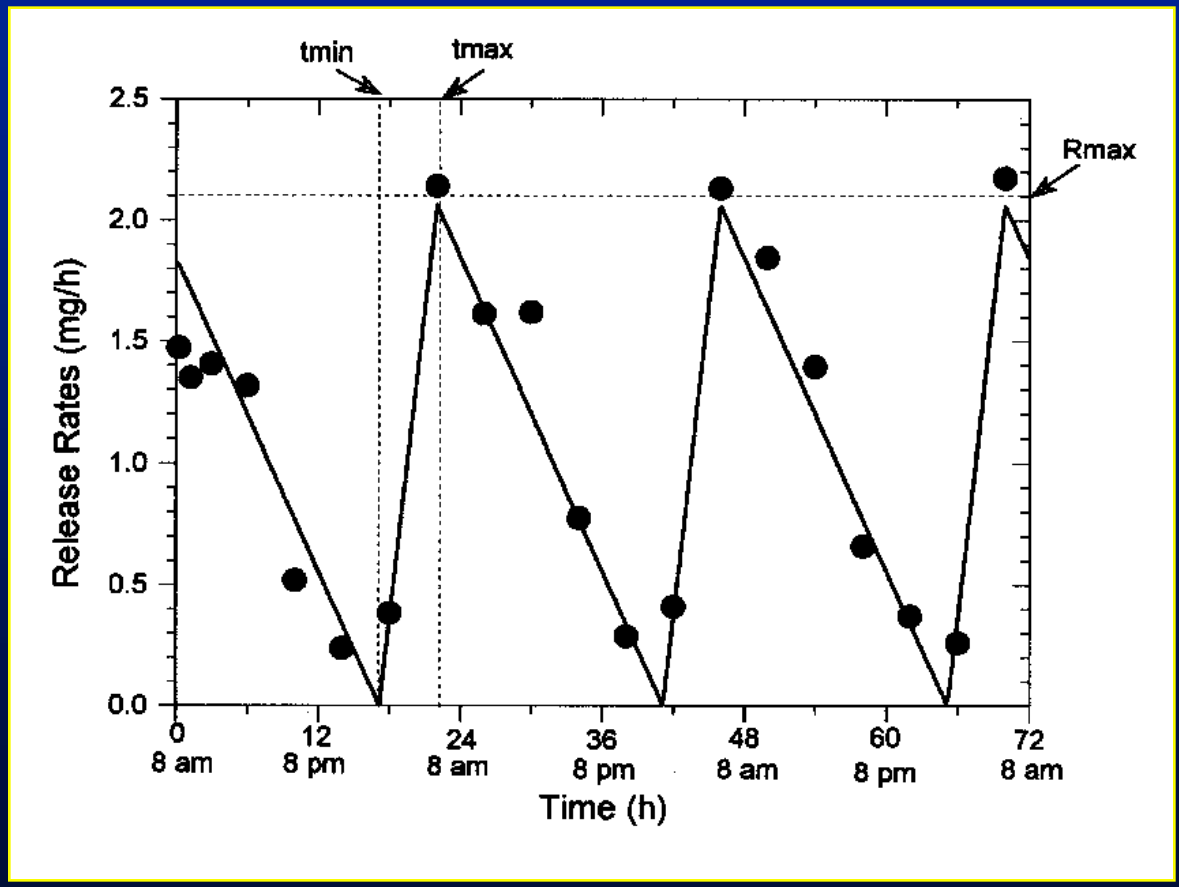
Derendorf H. *Respir Med.* 1997;91(suppl A):22-28;
Rohatagi S. et al.*J Clin Pharmacol* 2003;43:365-378.
ASMANEX TWISTHALER. Product Insert. 2003.

Plasma Protein Binding (cont'd)

- High protein binding of a high-extraction drug after inhalation results in low systemic unbound concentrations
- Only the free, unbound drug is pharmacologically active
- High protein binding for an inhaled corticosteroid can dramatically improve its risk-benefit ratio
- Ciclesonide is an inhaled corticosteroid with very high protein binding

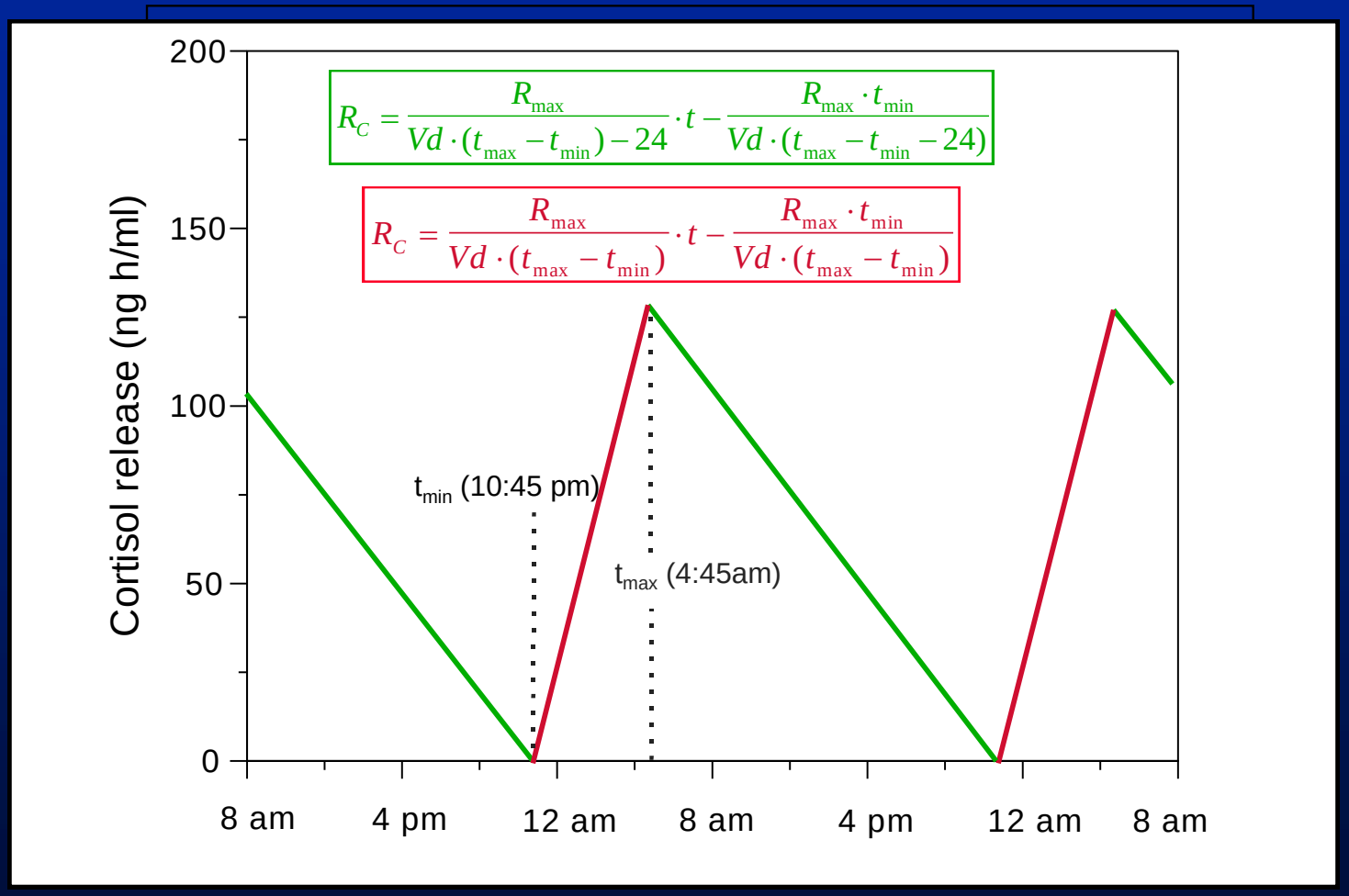
Cortisol Release Rate

determined by deconvolution of cortisol plasma levels



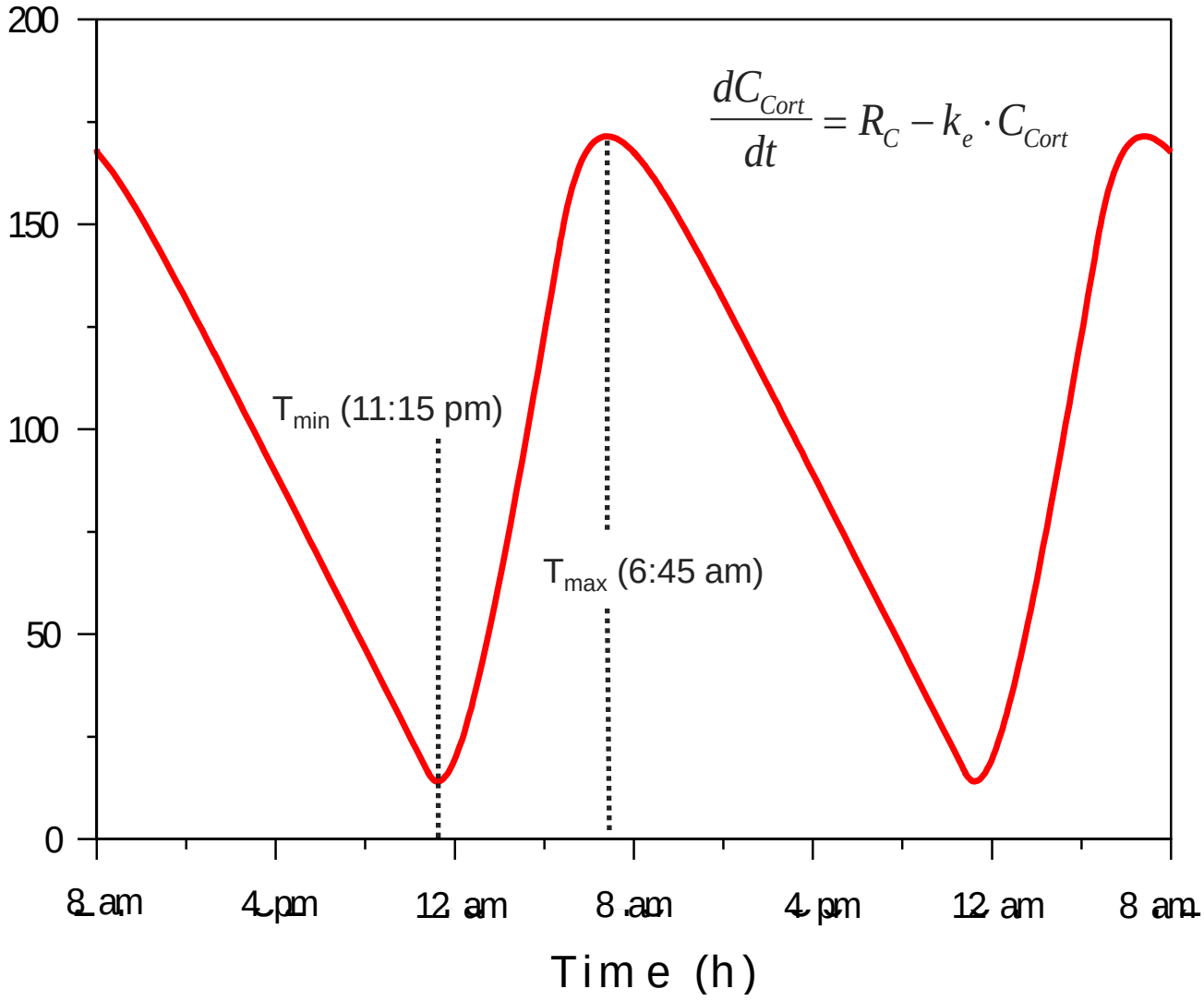
Cortisol Linear Release Model

Cortisol release



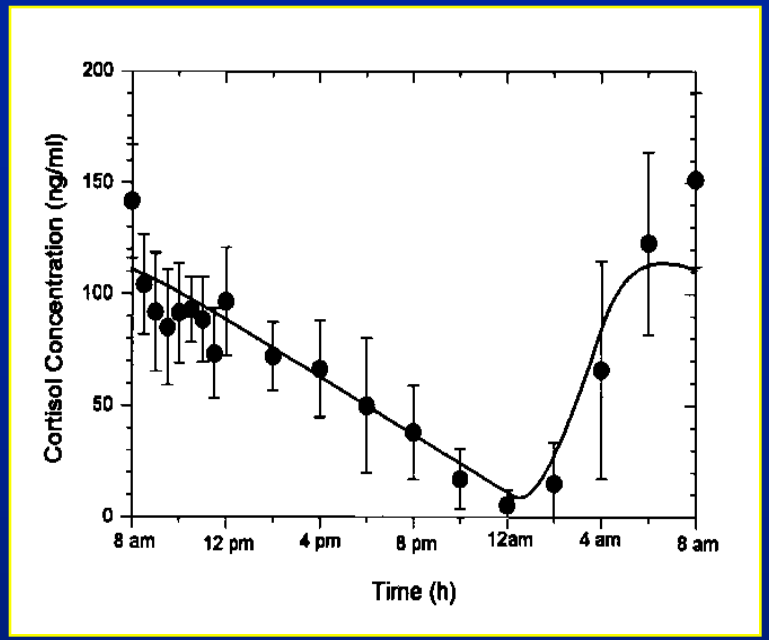
Cortisol Linear Release Model

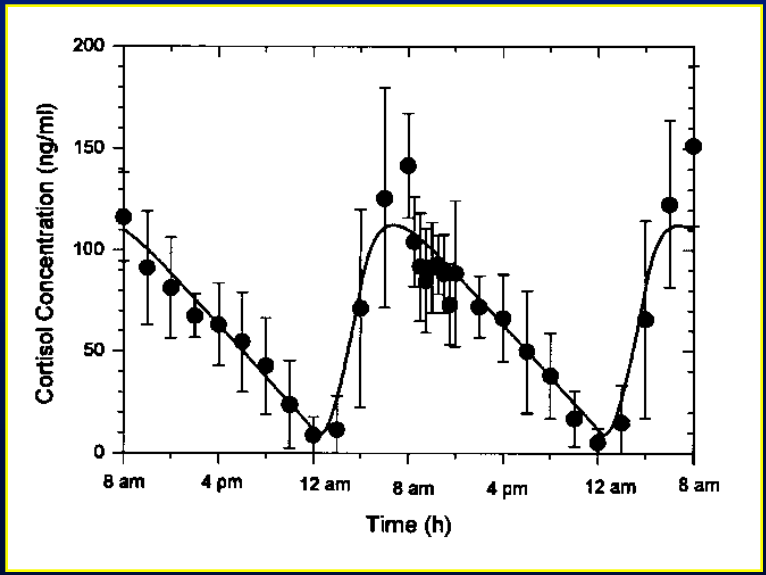
Cortisol plasma concentration

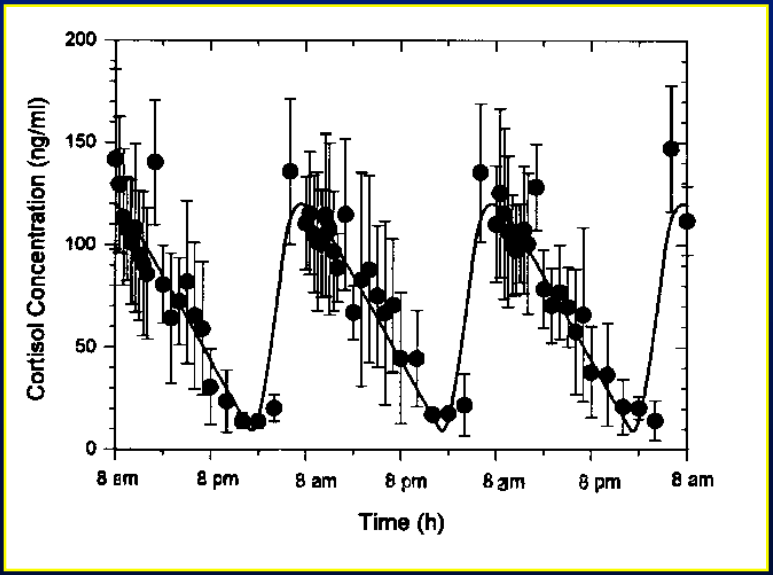


Cortisol Baseline

Over one, two and three days







Cortisol Linear Release Model

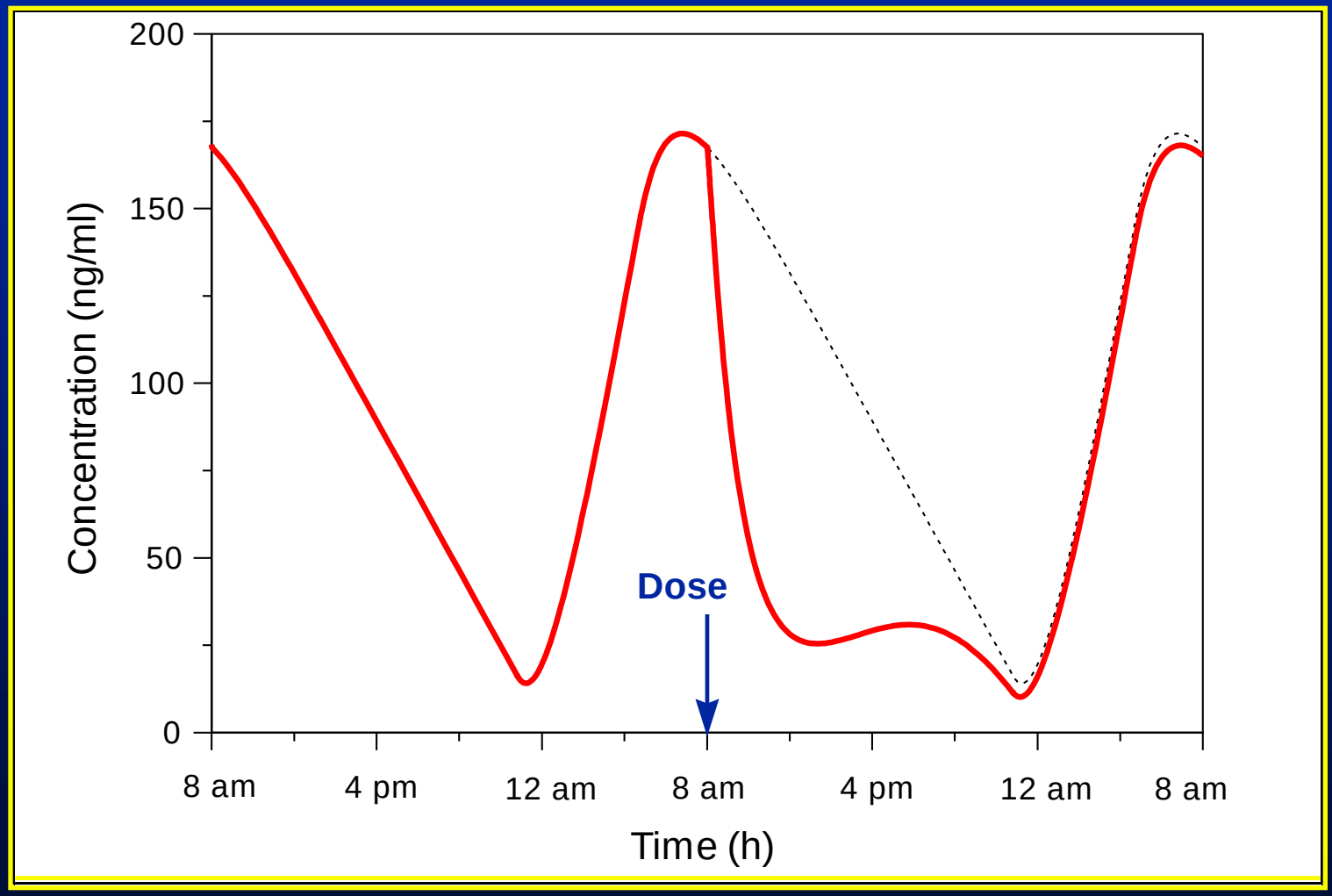
Cortisol linear release / E_{max} Model

$$\frac{dC_{Cort}}{dt} = R_C \cdot \left(1 - \frac{E_{\max} \cdot C_f}{EC_{50} + C_f}\right) - k_e \cdot C_{Cort}$$

R_c	Cortisol Release Rate [conc/time]
C_{Cort}	Cortisol Concentration
C_f	Unbound Concentration of Exogenous Steroid
k_e	Elimination Rate Constant of Cortisol
E_{max}	Maximum Effect (=1)
EC_{50}	C_f for Half-Maximum Effect

Cortisol Linear Release Model

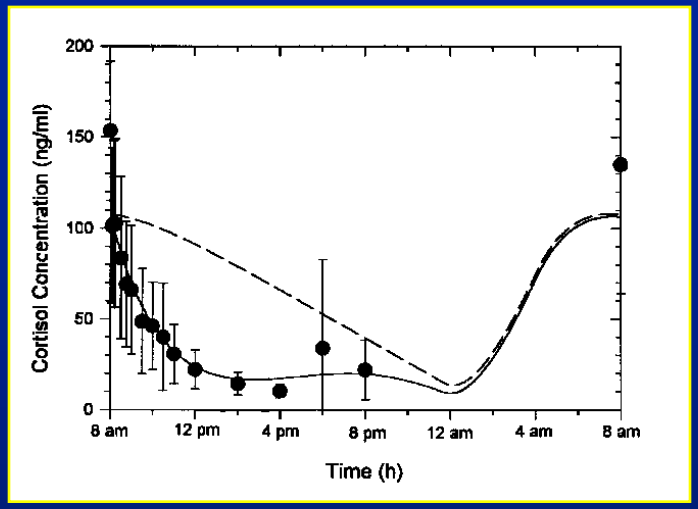
Cortisol plasma concentration



Cortisol Suppression
Triamcinolone Acetonide

- **intravenous administration (iv)**
  2 mg TCA phosphate
- **oral administration (po)**
  5 mg TCA in 100 ml ethanol (4 %)
- **pulmonary administration (inh)**
  2 mg TCA in 20 puffs over 5 minutes

iv



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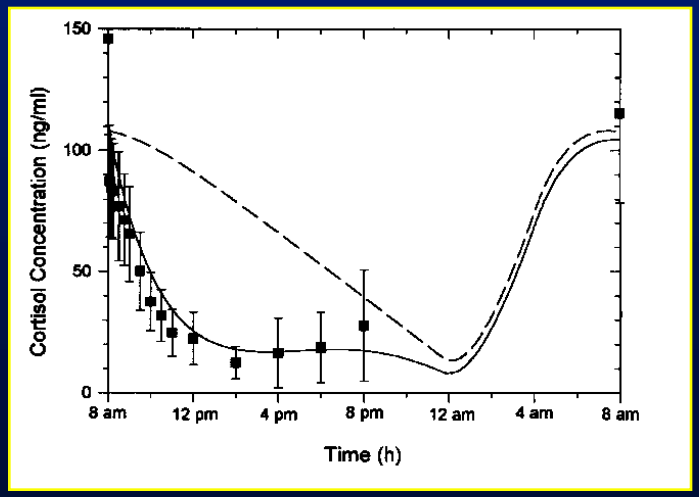
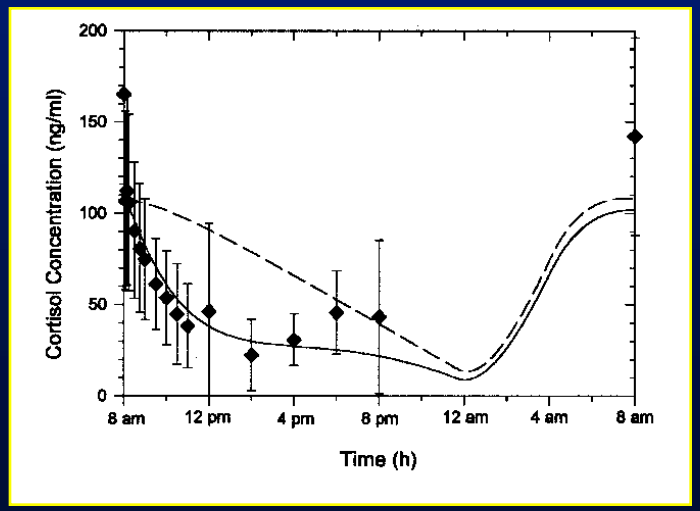
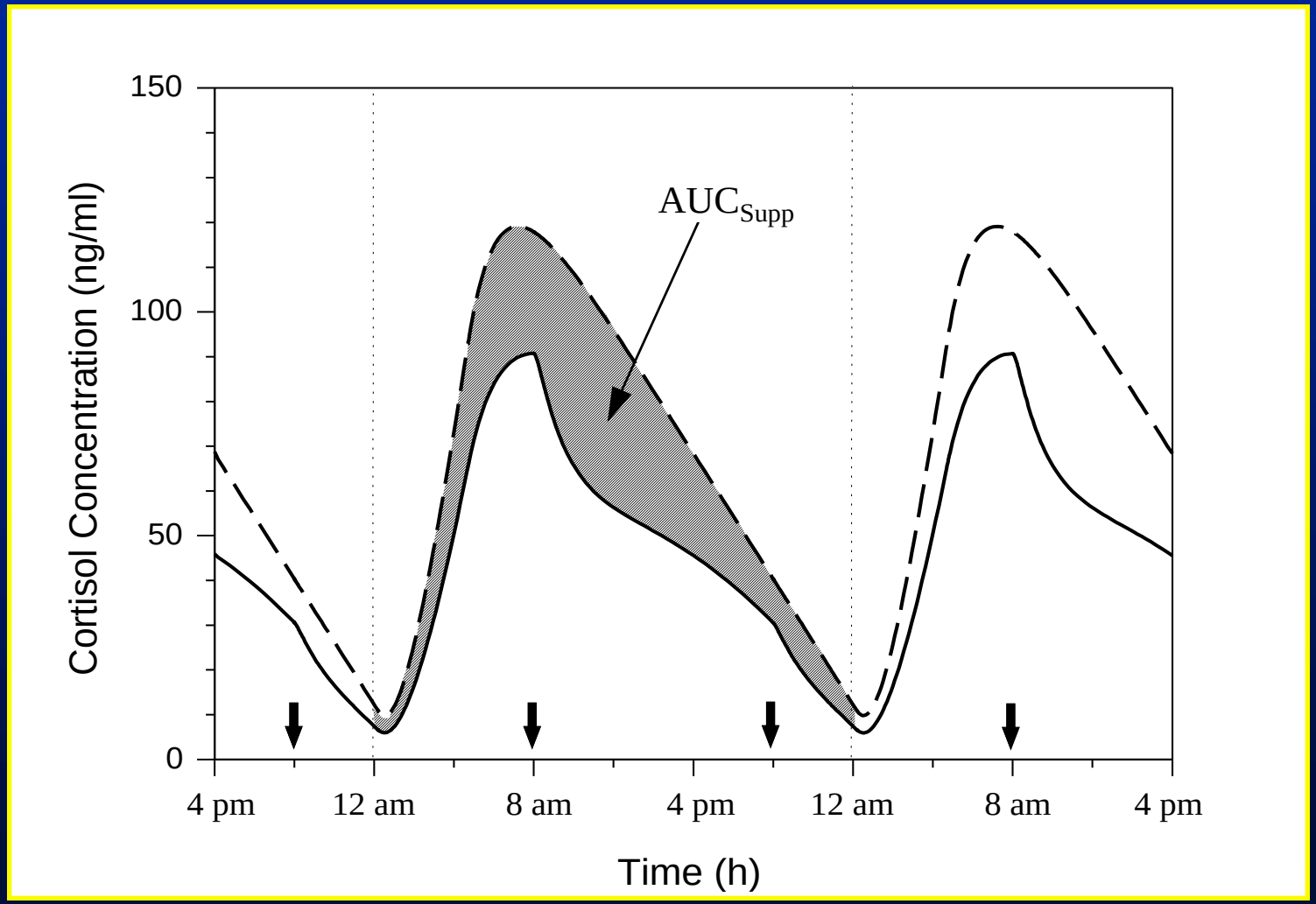


inh



Quantification of Cortisol Suppression

During Multiple Dosing



Microsoft Excel - CCS-singledose.xls

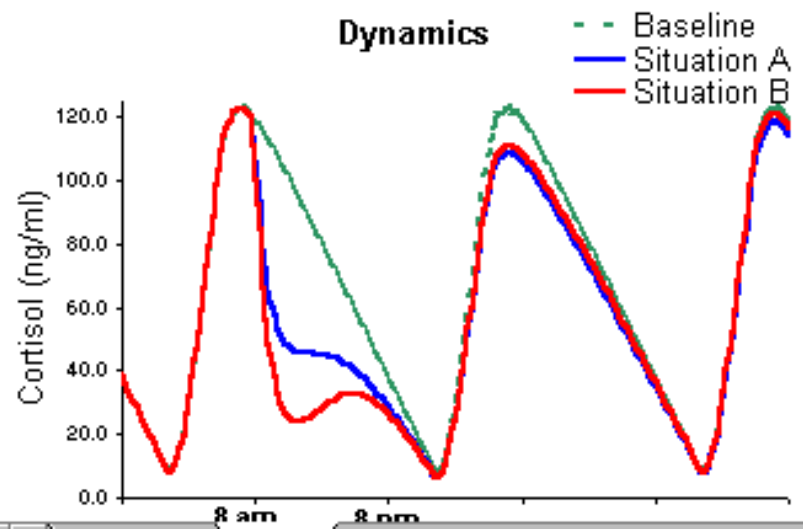
File Edit View Insert Format Tools Data Window Help

Arial 10 50%

O2 =

INPUT

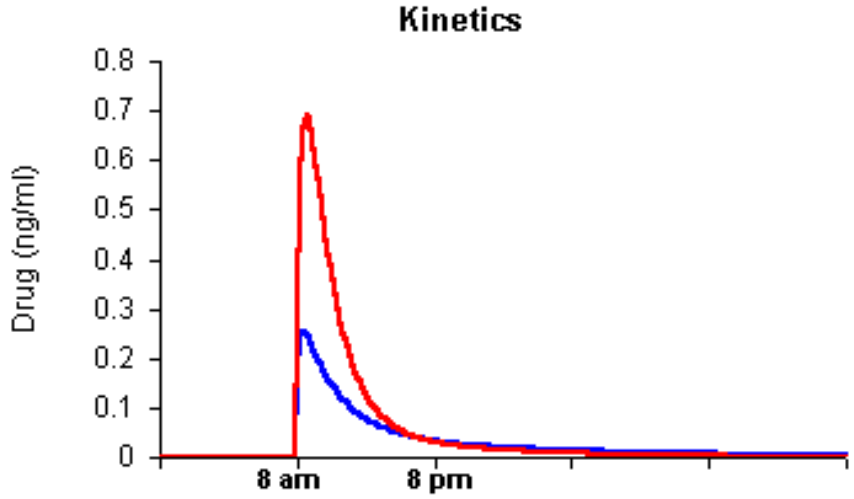
Situation	A	B
Drugs: FP, BUD, TA , FLU or ANY	FP	ANY
Enter dose (In micrograms)	500	1000
Enter time of dose (clock time)	8	8
Device (MDI=1, DH=2, DSKS=3, TBH=4)	1	4



OUTPUT

Cortisol suppression

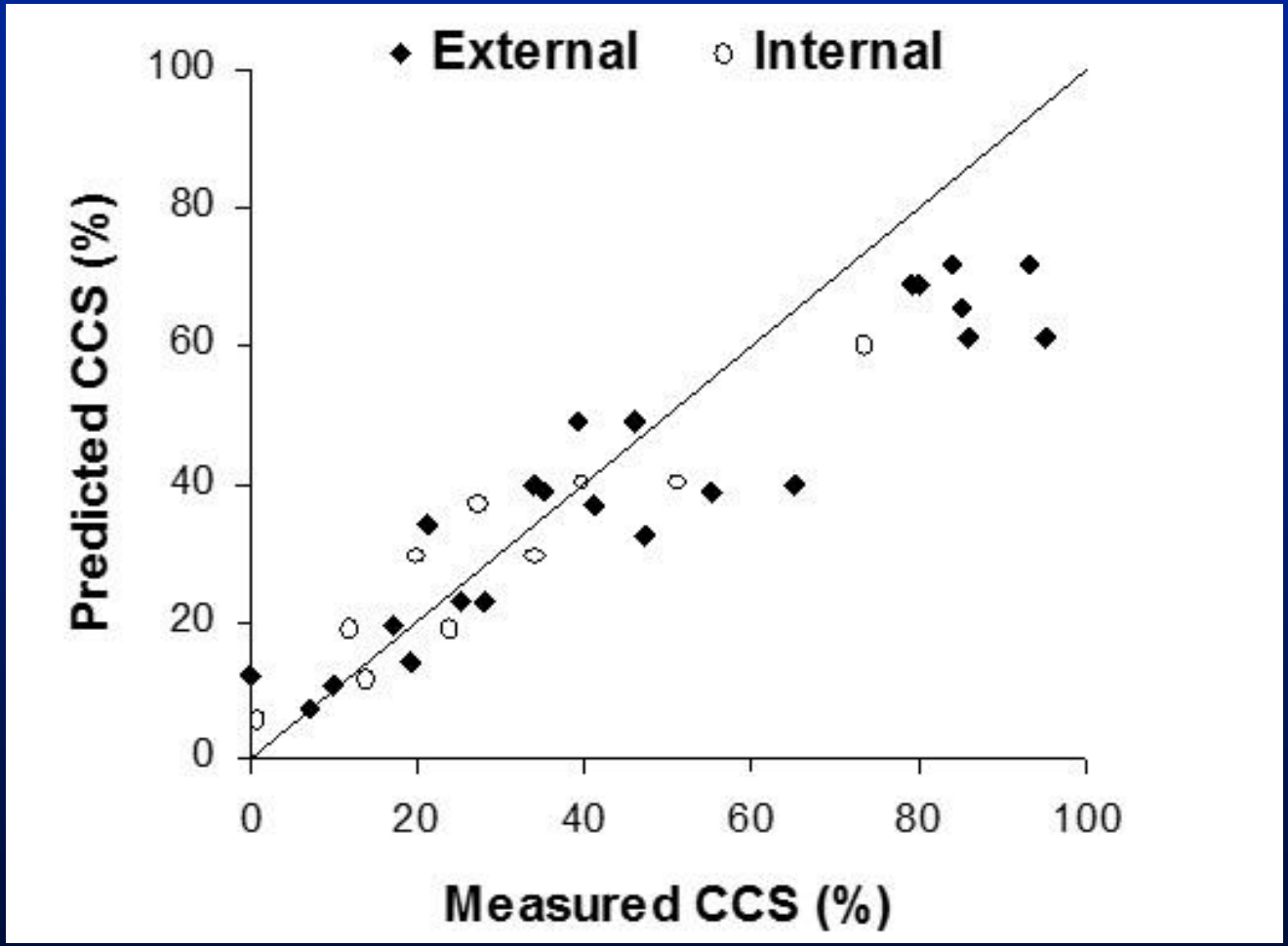
	A	B
CCS (%)	28.5	38.0



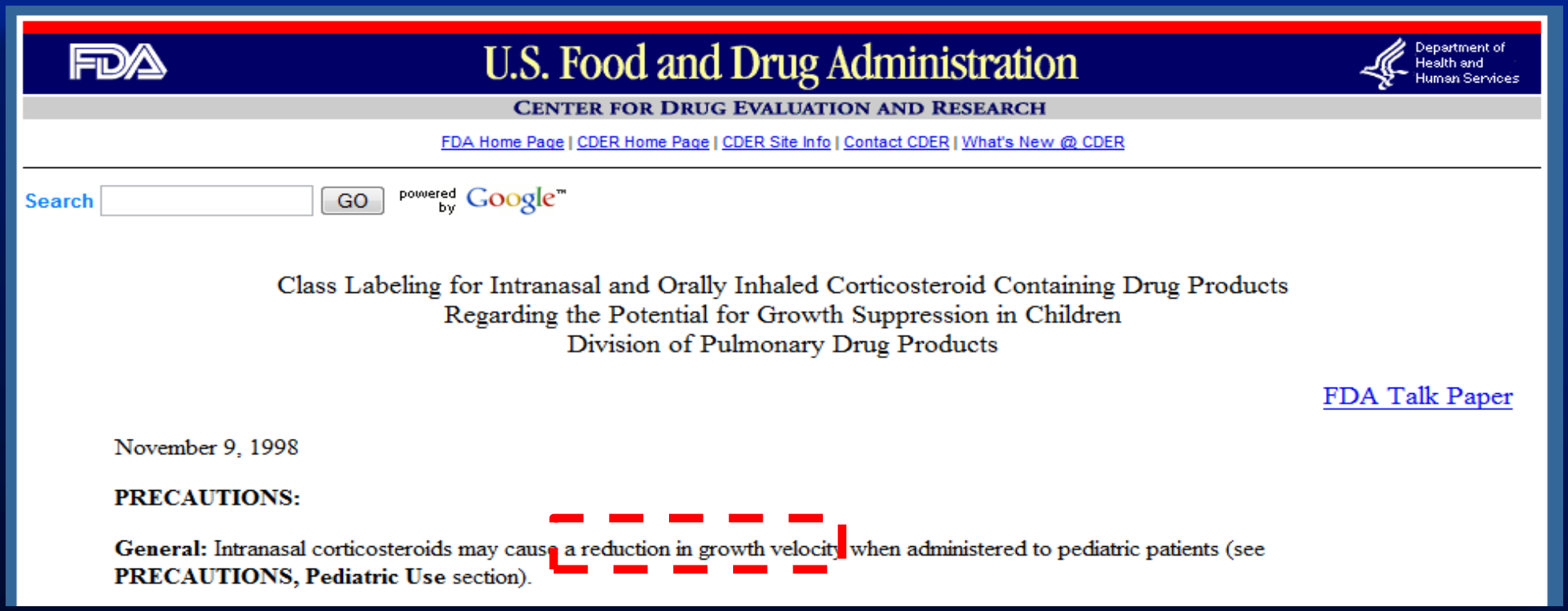
ANY DRUG | Input

Ready NUM

Predicted and Measured Cortisol Suppression: Multiple Dose



Current Labeling for ICSs



FDA U.S. Food and Drug Administration — Department of Health and Human Services

CENTER FOR DRUG EVALUATION AND RESEARCH

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Class Labeling for Intranasal and Orally Inhaled Corticosteroid Containing Drug Products
Regarding the Potential for Growth Suppression in Children
Division of Pulmonary Drug Products

FDA Talk Paper

November 9, 1998

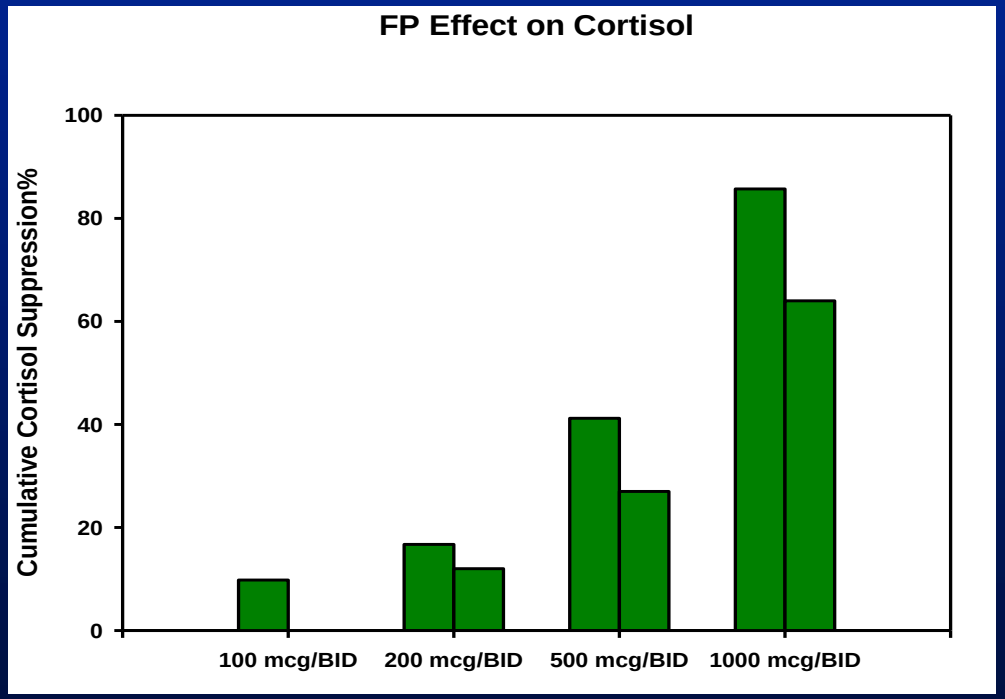
PRECAUTIONS:

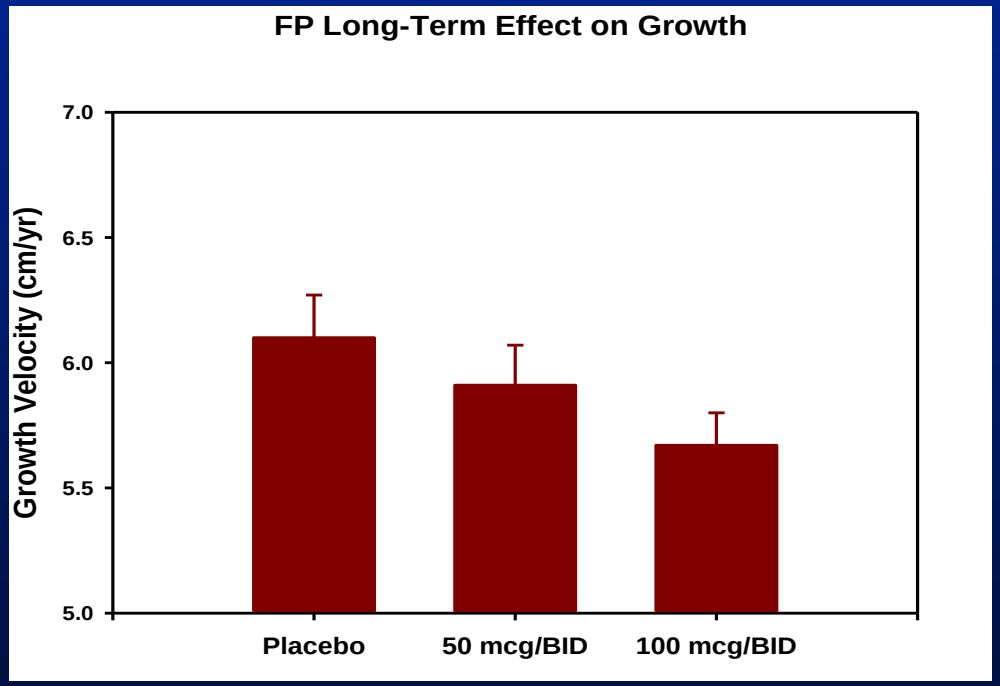
General: Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see **PRECAUTIONS, Pediatric Use** section).

Growth Assessment

- Length (first 2 years)
- Height
  - Stadiometry during childhood
    - Long-term growth (>3 years)
    - Intermediate-term growth (>12 months)
  - Predicted adult height and final adult height
- Low leg length (Knemometry)
  - Short-term growth
  - Poor reproducibility

Fluticasone propionate



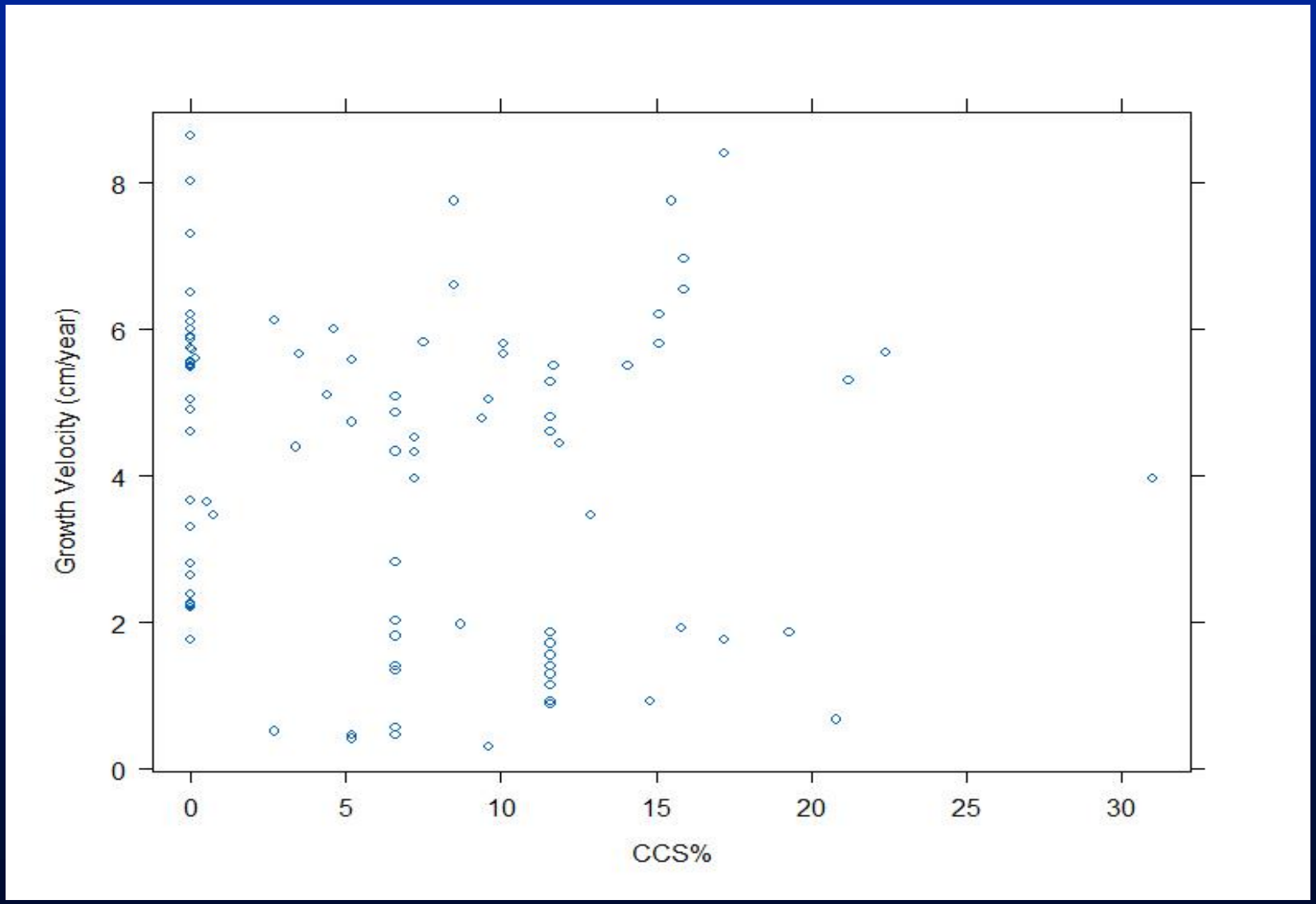


Grahnen A et al. *Eur. J. Clin. Pharmacol* 1997;52:261-7
Mollmann H et al. *J. Clin. Pharmacol* 2001;41:1329-38
Thorsson L et al. *Br. J. Clin. Pharmacol* 2001;52: 529-38
Allen DB et al. *J. Pediatr.* 1998;132:472-7

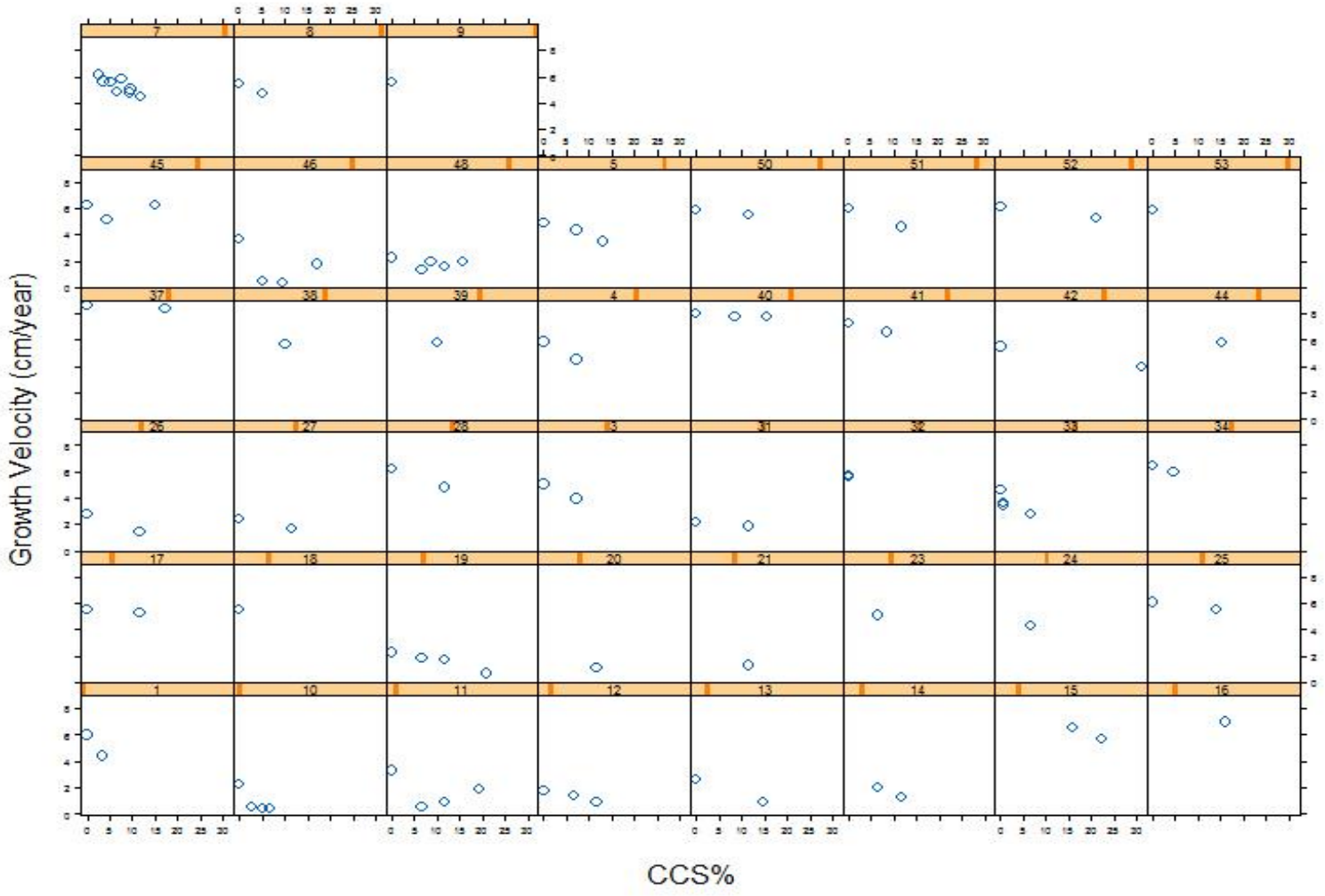
ICS and Growth Retardation

- Total 33 references were located with available information, and total 53 study records were created accordingly.
- Each ICS, including BDP, BUD, FP, CIC, MF, TAA, FLU, has at least one clinical study, which was conducted for growth effects.

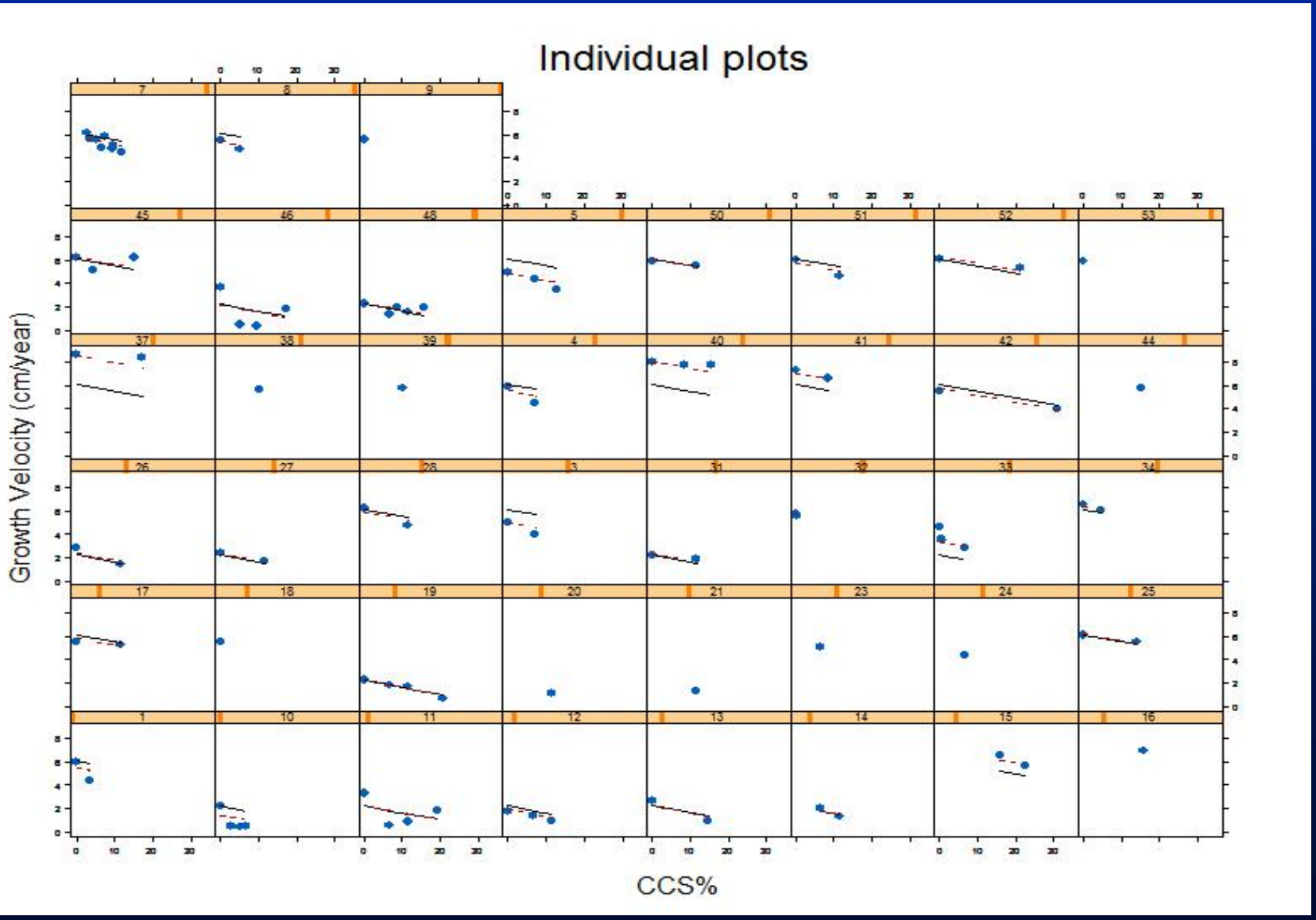
Results (Growth Velocity – CCS%)



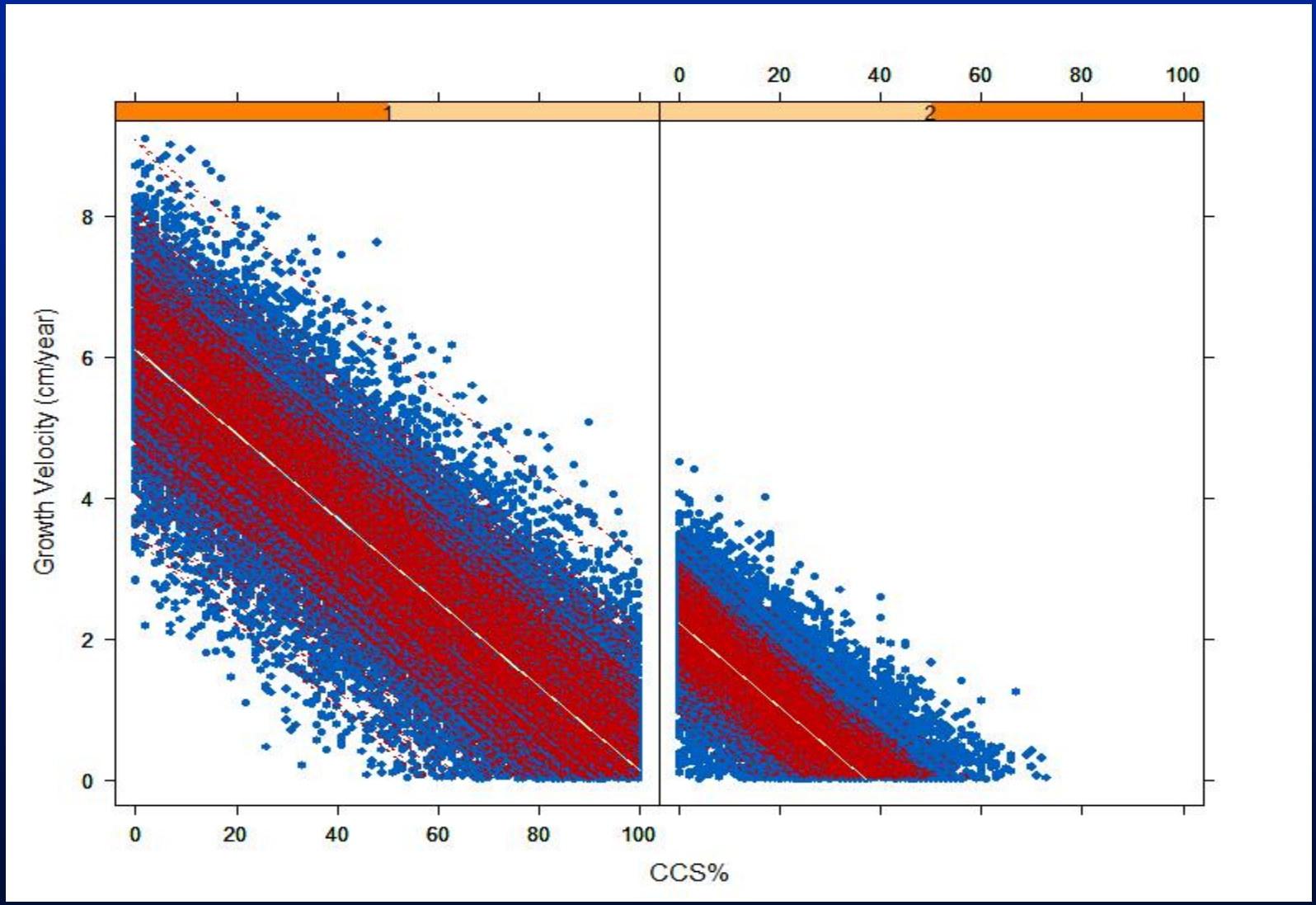
Results (Individual)



Results (NONMEM®)



Results (Simulations)



Prediction of Change of GV

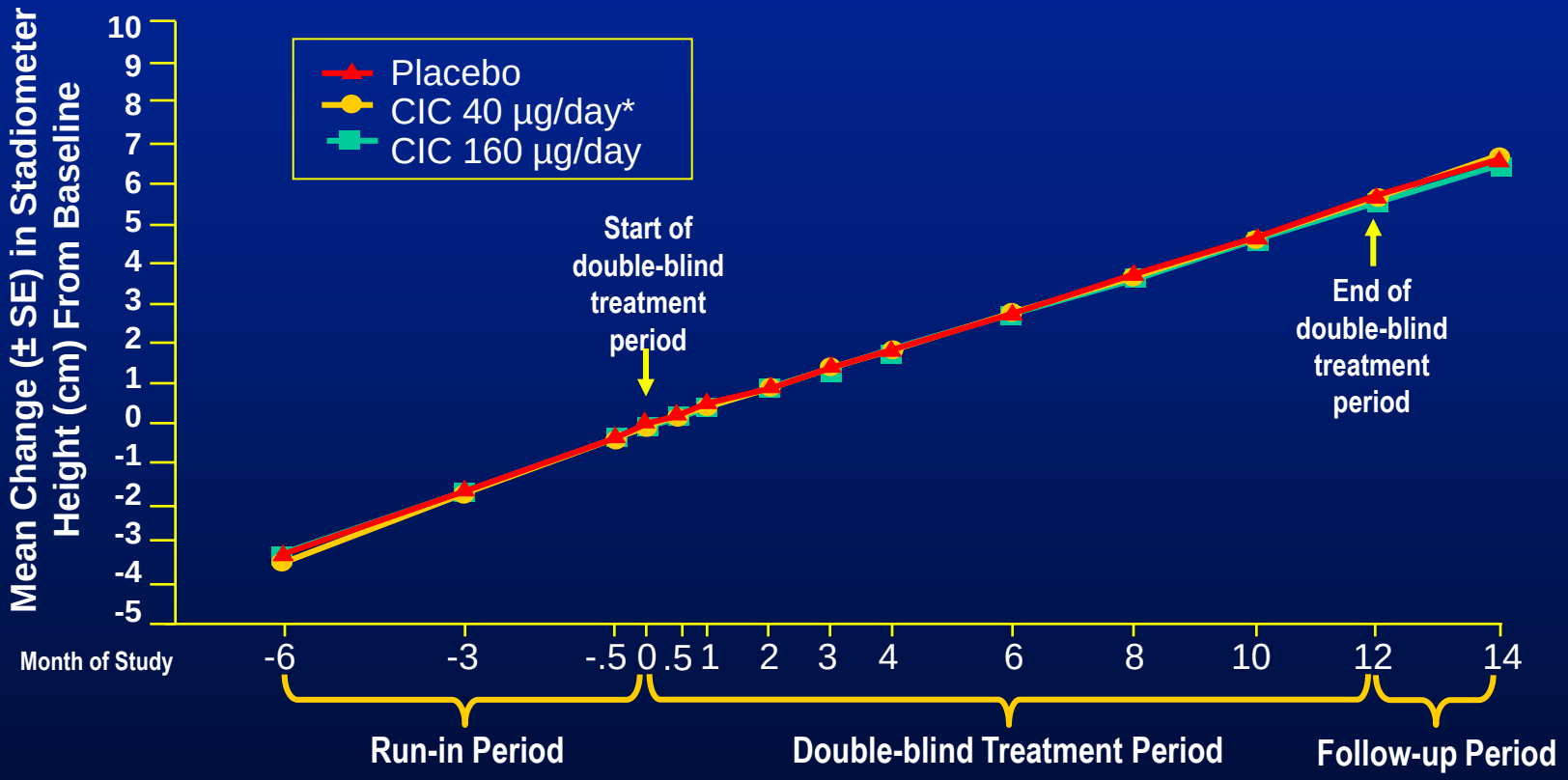
Drug Name [n]	Brand Name [o]	Age of Patients [o]	Dosing Regimen [o]	Estimated CCS % [p]	Predicated ΔGV (cm/year) [q]
BDP	QVAR®	5-11 years	40 µg BID	2.80%	0.17
			80 µg BID	5.40%	0.32
BUD	PULMICORT® FLEXHALER®	6-17 years	180 µg BID	10.70%	0.64
			360 µg BID	18.00%	1.08
	PULMICORT® RESPULES®	1-8 years	500 µg QD	12.50%	0.75
			250 µg BID	10.30%	0.62
			1000 µg QD	19.10%	1.15
			500 µg BID	17.40%	1.04
CIC	ALCESCO®	>12 years	80 µg QD	0.07%	0.004
			160 µg QD	0.15%	0.009
FLU	AEROBID®	6-15 years	500 µg BID	26.90%	1.61
FP	FLOVENT® DISKUS®	4-11 years	50 µg BID	6.30%	0.38
			100 µg BID	11.70%	0.70
MF	ASMANEX® TWISTHALER®	4-11 years	110 µg QD	3.10%	0.19
TAA	AZMACORT®	6-12 years	75 µg TID	10.30%	0.62
			150 µg BID	11.70%	0.70
			300 µg BID	20.20%	1.21
			150 µg QID	16.00%	0.96
			300 µg TID	30.70%	1.84

[n]: drug abbrevations; [o]: From product inserts

[p]: CCS%: cumulative cortisol suppression within 24 hr at steady state; estimated with the published algorithm

[q]: ΔGV: change of growth velocity compared to the placebo, or run-in period, or active control, or baseline; predicted with population estimates in the final model

Ciclesonide



* Pediatric dose TBD.

Skoner D. Poster presented at: American Academy of Allergy, Asthma & Immunology. Miami Beach, Florida;2006.

Efficacy

- Linked to local exposure at the target site (intracellular steroid receptors in the lung)
- How much drug gets into the lung and where in the lung is it deposited?
  - (Deposition)
- How long does the drug stay in the lung?
  - (Residence time)

Pulmonary Deposition: Factors Relevant for Pulmonary Deposition

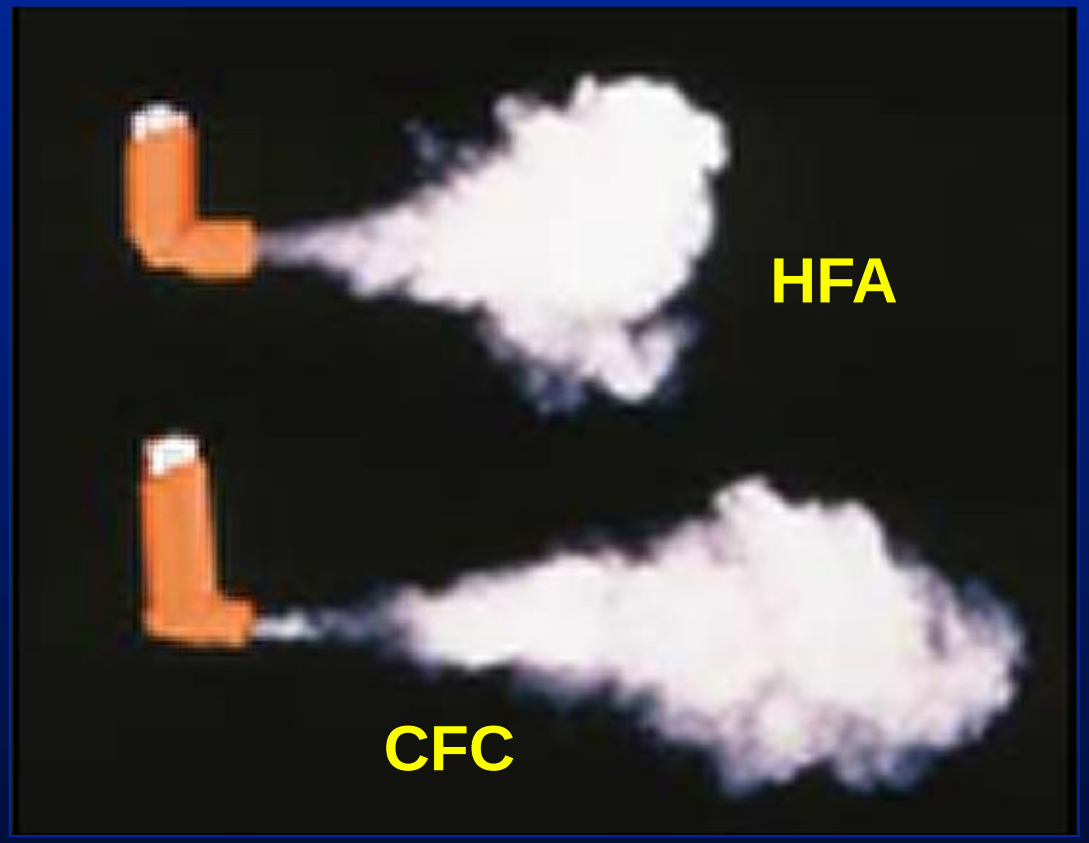
- Inhaled particles (size, shape, density, hygroscopy, charge, velocity)
- Device (principle and design features such as DPI/MDI/nebulizer, spacer vs nonspacer, HFA/CFC devices, etc.)
- Patient (lung anatomy, breathing pattern, disease state, technique, mucociliary transport)

Pulmonary Deposition

MDI	10%–15%
Diskus® DPI	14%–20%[1]
Diskhaler®	10%–15%
MDI with spacer	15%–25%
Turbuhaler®	20%–30%[2]
QVAR®	60%[3]
Respimat®	40%[4]
Ciclesonide	50%[5]

1. Mackie AE, et al. *Br J Pharmacol.* 1997;120(suppl):P249. 2. Thorsson L, et al. *Eur Respir J.* 1994;7:1839-1844. 3. Leach CL, et al. *Eur Resp J.* 1998;12:1346-1353. 4. Newman SP, et al. *Chest.* 1998;113:957-963. 5. Bethke TD, et al. Poster presented at the European Respiratory Society Congress, Stockholm. Sept. 15, 2002.

BDP: HFA vs CFC



Result:

- Smaller particle size (1-2 mm vs 2-5 mm)
- Higher pulmonary deposition
- More peripheral deposition

3M website.

Gamma Scintigraphy
BDP: CFC vs HFA

CFC-BDP **HFA-BDP**

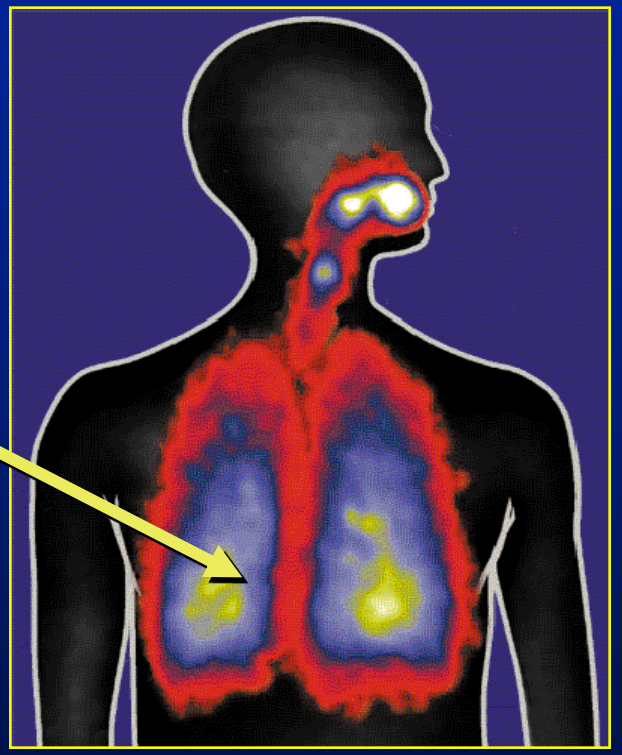
3M information.

Lung Deposition of Inhaled Corticosteroids

Dose to the Lungs
Ciclesonide

	%
Fluticasone DPI	**12**
Fluticasone CFC-MDI	**12–20**
Budesonide CFC-MDI	**15–18**
Budesonide DPI	**15–28, 32–42**
Mometasone HFA-MDI	**14**
BDP HFA-MDI	**53–60**
BDP CFC-MDI	**4–7**
BDP DPI	**19**

HFA-MDI 52%[1,2]

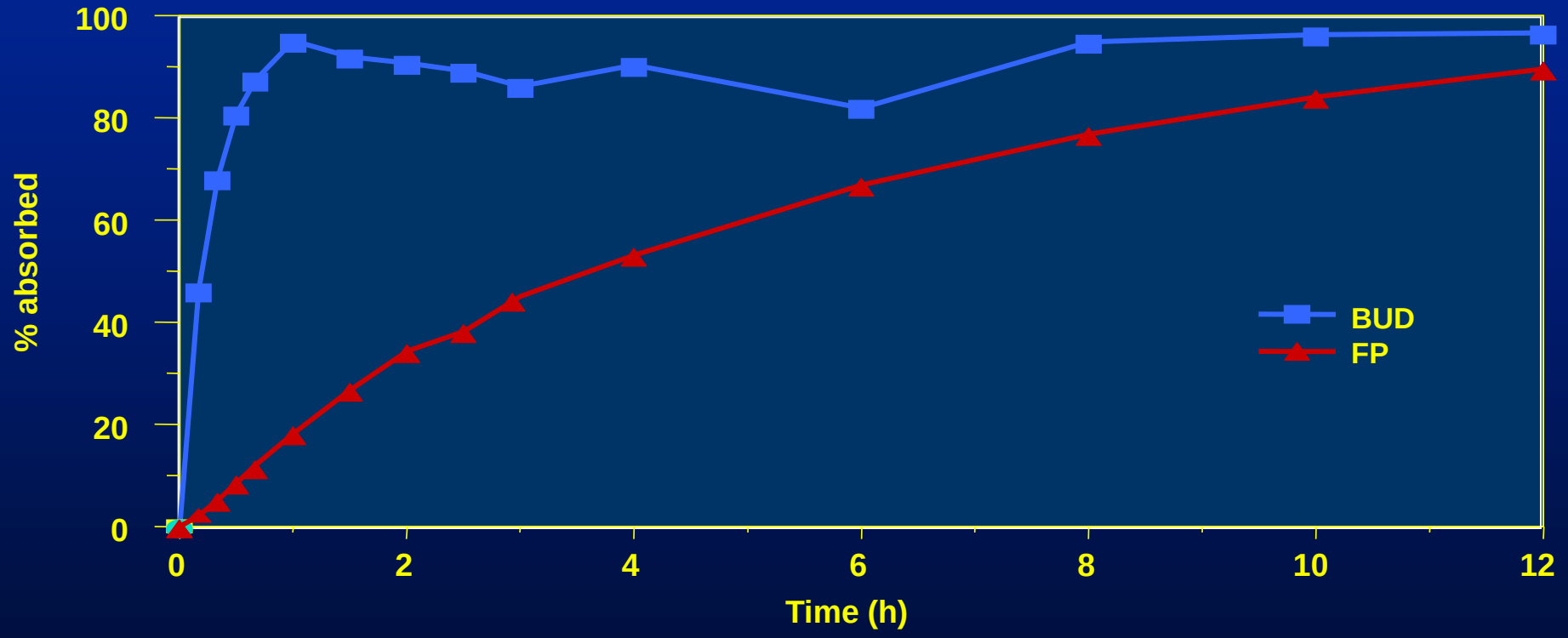


Deposition characteristics of ^{99m}Tc-labeled CIC (ex-actuator)

Bethke T, et al. *Eur Respir J*. 2002;38:109S; Newman et al. *Eur Respir J.* 2004;24:583S; Thorsson L, et al. *Br J Clin Pharmacol.* 2001;52:529-538; Leach CL, et al. *Chest*. 2002;122:510-516; Thorsson L, et al. *Eur Respir J.* 1994;7:1839-1844; Hirst PH, et al. *Respir Med*. 2001;95:720-727; Borgström L, et al. *Eur Respir J.* 1994;7:69-73; Pickering H, et al. *Clin Ther.* 2000;22:1483-1493; Leach CL, et al. *Eur Respir J*. 1998;7:1839-1844; Newman et al. *J Aerosol Med.* 2001;14:217-225.

Pulmonary Residence Time

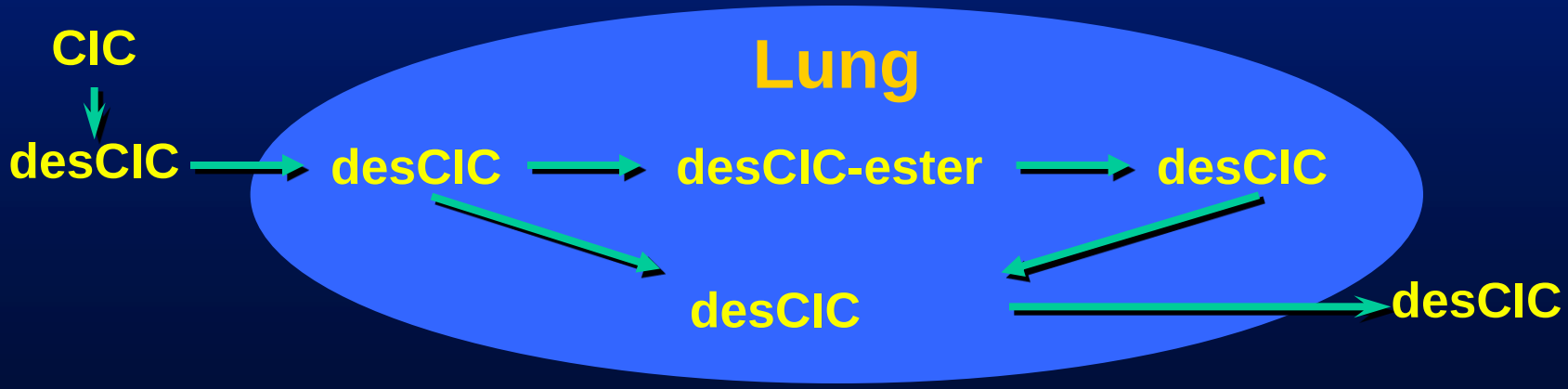
Absorption Profiles of Inhaled Corticosteroids



Meibohm B, et al. 12th Annual Meeting of the American Association of Pharmaceutical Scientists, Boston, Mass. November 1997.

Lipid Conjugation

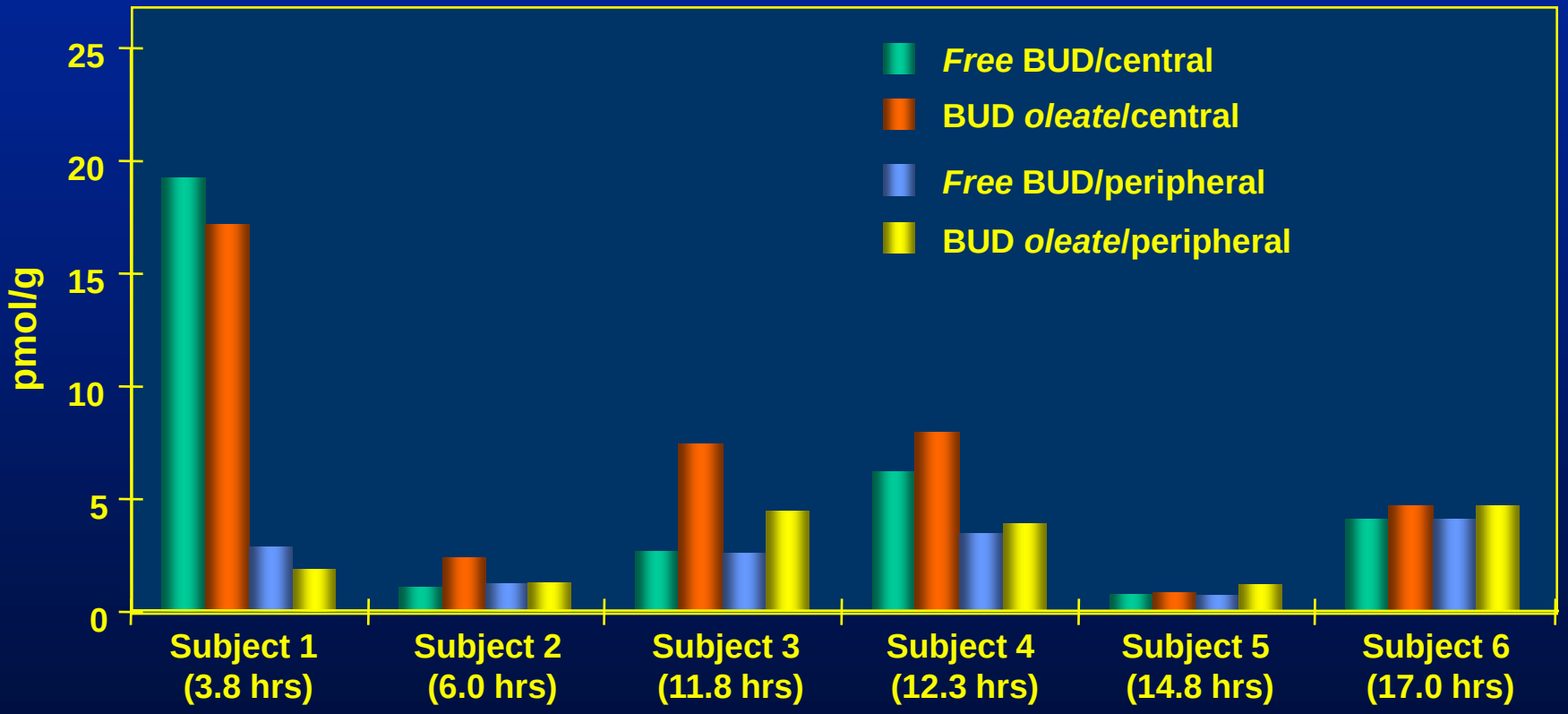
- Corticosteroids with a hydroxyl group in C-21 can form esters with fatty acids in the lung
- These lipid conjugates increase the pulmonary residence time of the corticosteroids and provide a local depot for their slow release



Nave R, et al. ATS International Conference, Seattle, Wash, May 16-21, 2003.

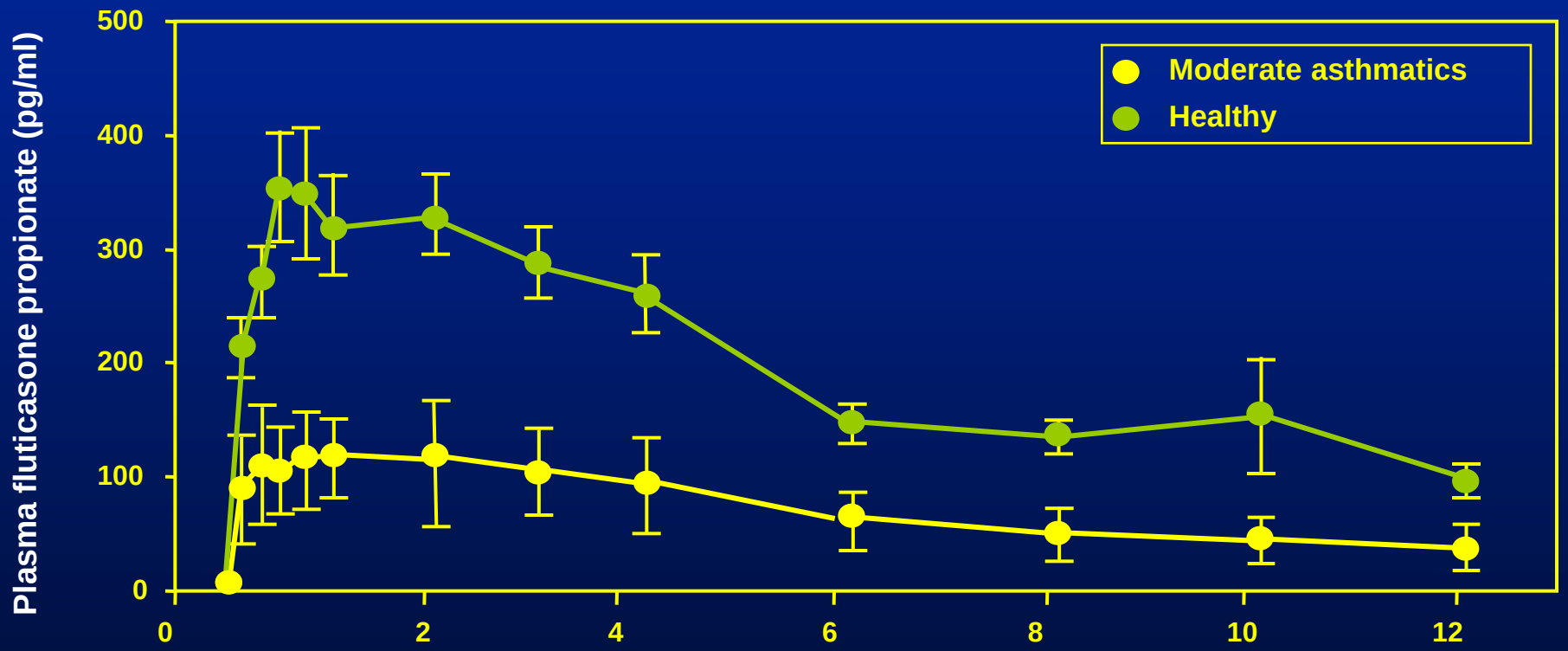
In Vivo Kinetics of Fatty Esters

Central and Peripheral Lung – 6 patients undergoing lung lobe resection



Thorsson et al. 1998.

Effect of Disease



Area under the curve for plasma fluticasone propionate concentration after inhalation

Brutsche MH, et al. *Lancet.* 2000;356:556-561.

Effect of Disease

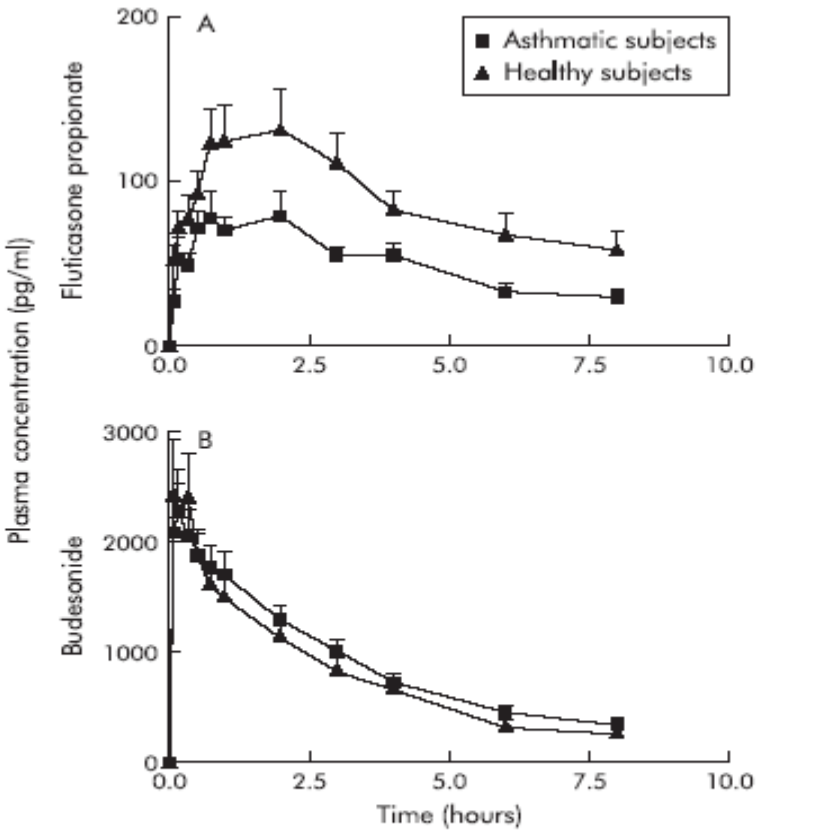


Figure 1 Mean (SE) plasma concentrations of (A) fluticasone propionate and (B) budesonide in healthy subjects and subjects with moderately severe asthma.

Harrison TW, Tattersfield AW, *Thorax* 2003;58:258-260

Adherence

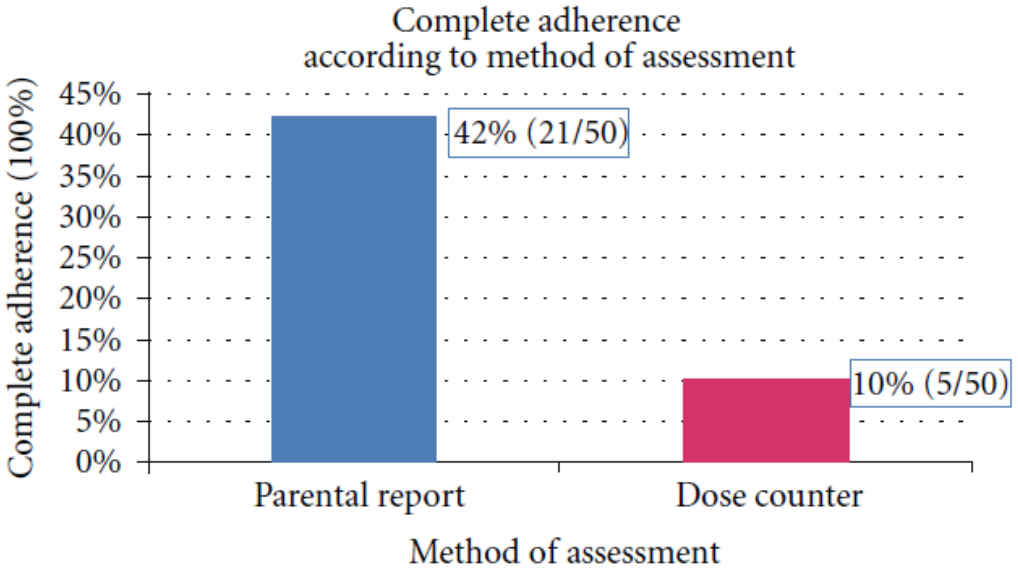


Table 2 3-Year mortality rates in patients with COPD with good or poor adherence.[82]

Therapy	3-Year mortality rates (%)	
	Good adherence	Poor adherence
Salmeterol	10.7	25.2
Fluticasone propionate	12.9	28.7
Combination salmeterol/ fluticasone propionate	9.5	24.9
Placebo	12.0	26.7

Good adherence was defined as an average adherence to study medications of >80% over the whole period the subject was in the study; poor adherence was defined as ≤80%.

Reznik, Ozua, J.of Allergy (2012)
Vestbo et al, Thorax (2009)

PK/PD Features of the Ideal ICS

- High respirable fraction
- High receptor binding
- Lipid conjugation

High potency/efficacy

- Small particle size
- Pro-drug moiety

Negligible oropharyngeal effects

- Low oral bioavailability
- High systemic clearance
- No active metabolites
- High plasma protein binding

Negligible systemic effects

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Delayed Release Prednisone

ACCP
American College of Clinical Pharmacology
Advancing Clinical Care through Pharmacology®

The Journal of Clinical Pharmacology
XX(X) 1–8

DOI: 10.1177/0091270012444315
http://jcp.sagepub.com
SAGE

Pharmacokinetics of Modified-Release Prednisone Tablets in Healthy Subjects and Patients With Rheumatoid Arthritis

Hartmut Derendorf, PhD[1], Klaus Ruebsamen, PhD[2], Lynsey Clarke, MBBS[3], Achim Schaeffler, PhD[2], and John R. Kirwan, BSc, MD[3]

Delayed Release Prednisone

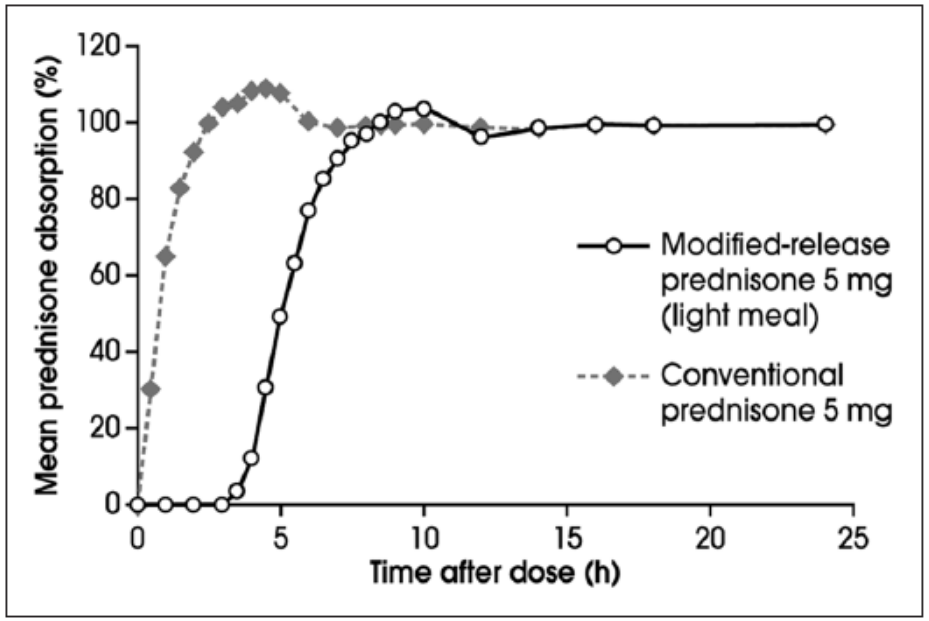


Figure 1. Absorption of prednisone after a single oral dose of conventional prednisone 5 mg and modified-release prednisone 5 mg

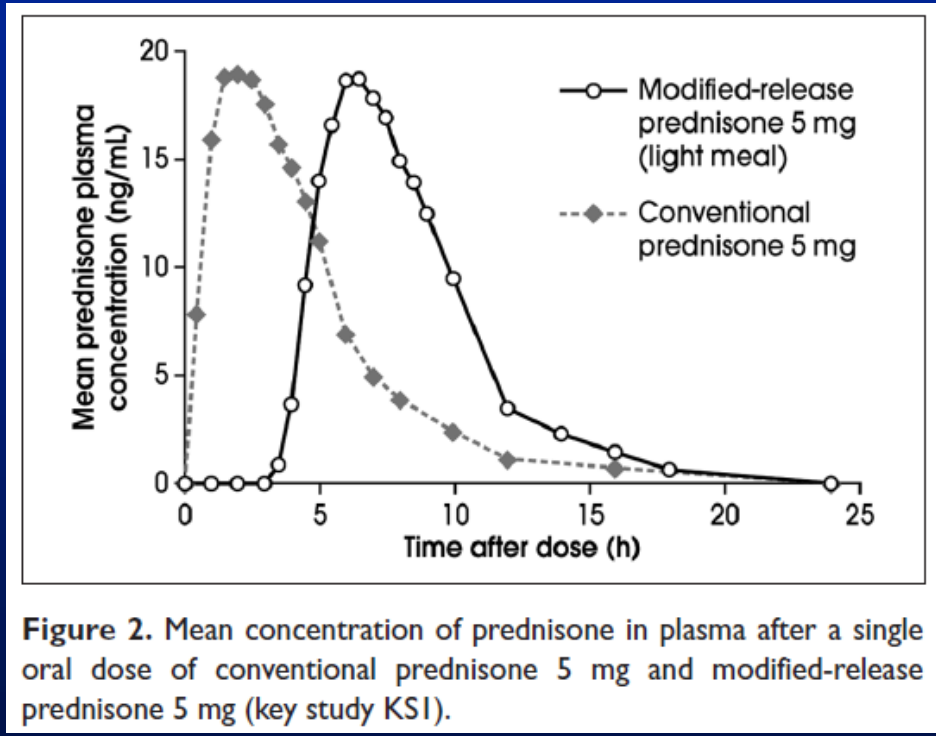
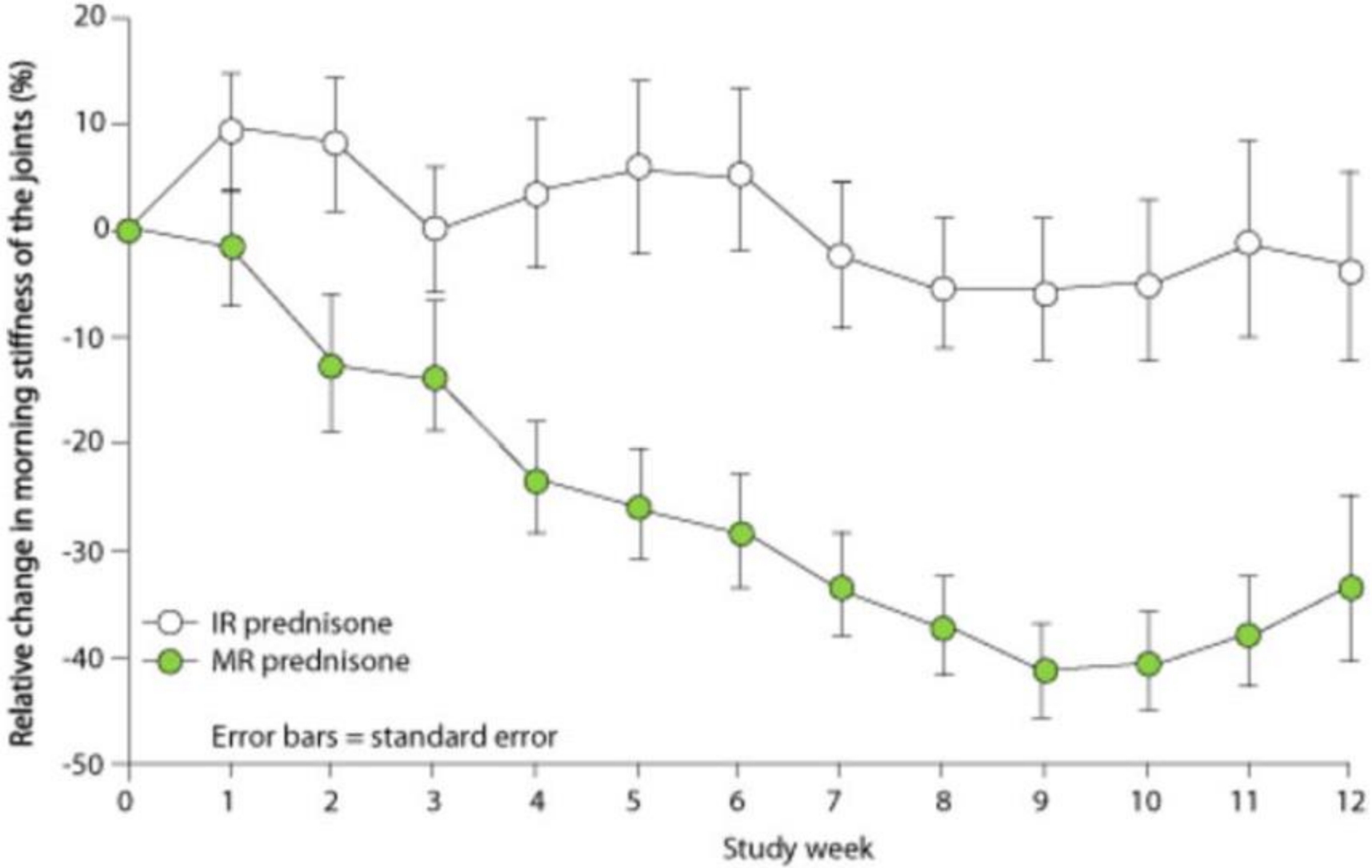


Figure 2. Mean concentration of prednisone in plasma after a single oral dose of conventional prednisone 5 mg and modified-release prednisone 5 mg (key study KS1).


Relative change in morning stiffness of the joints (%)
20
10
0
-10
-20
-30
-40
-50
IR prednisone
MR prednisone
Error bars = standard error
0
1
2
3
4
5
6
7
8
9
10
11
12
Study week

Bioequivalence Studies for Orally Inhaled and Nasal Drugs: An FDA Perspective

Wallace P. Adams, Ph.D.

OPS/CDER/US FDA

ACCP 32nd Annual Meeting

Palm Harbor (Tampa), FL

21 September 2003

This presentation represents the personal opinions of the speaker and does not necessarily represent the views or policies of the US FDA.

Locally Acting Drug Products (OINDP)*

The Bioequivalence Problem:

In general, pharmacokinetic studies are by themselves insufficient to establish BE

*Orally inhaled and nasal drug products (OINDP)

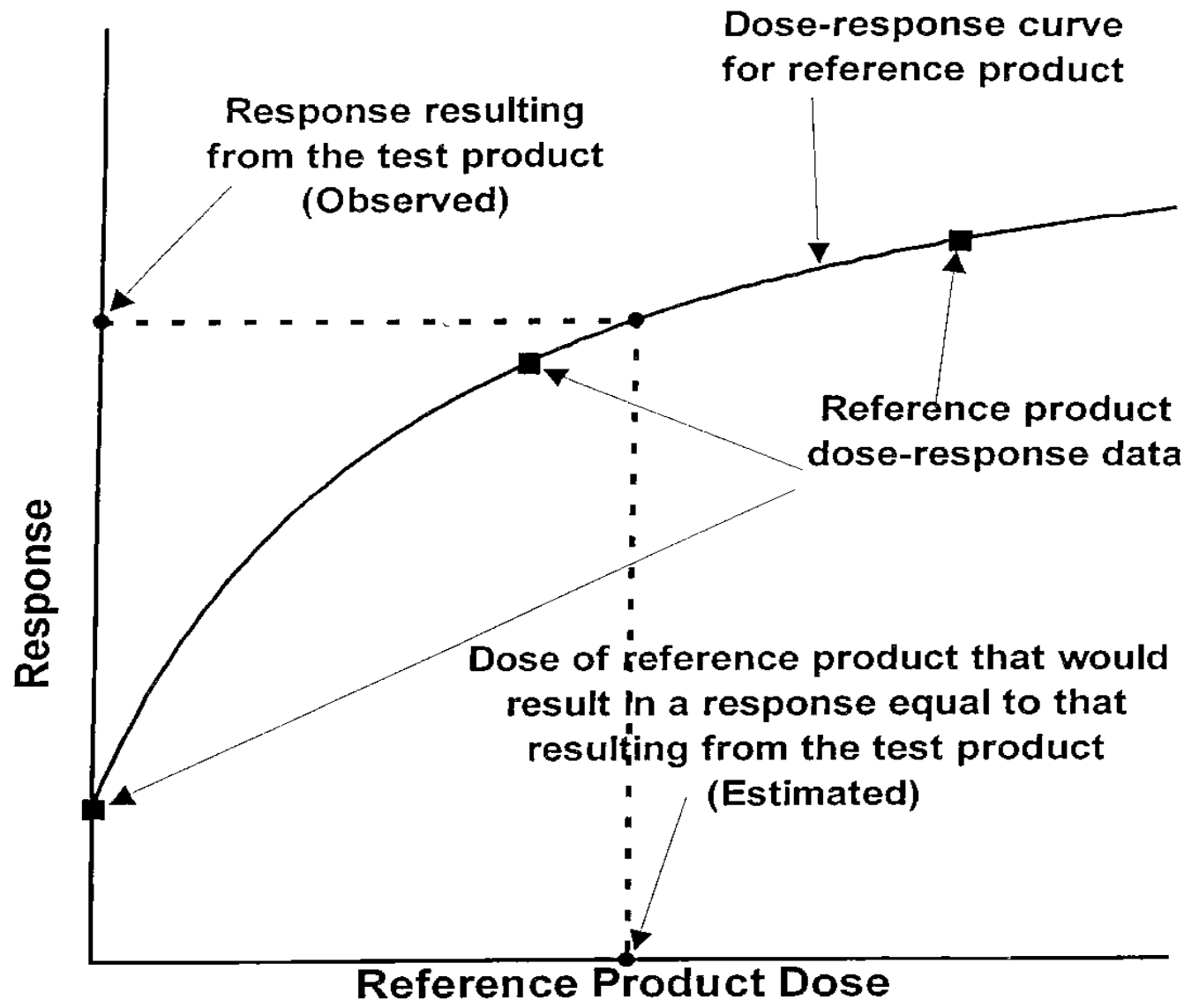
Bioequivalence of Inhaled Corticosteroids

Bioequivalence – FDA Definition

21 CFR 320.1

"Absence of a significant difference in the rate and extent to which the active ingredient or active moiety in *pharmaceutical equivalents* or *pharmaceutical alternatives* becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study"

BE Criteria on the Dose Scale: Theory

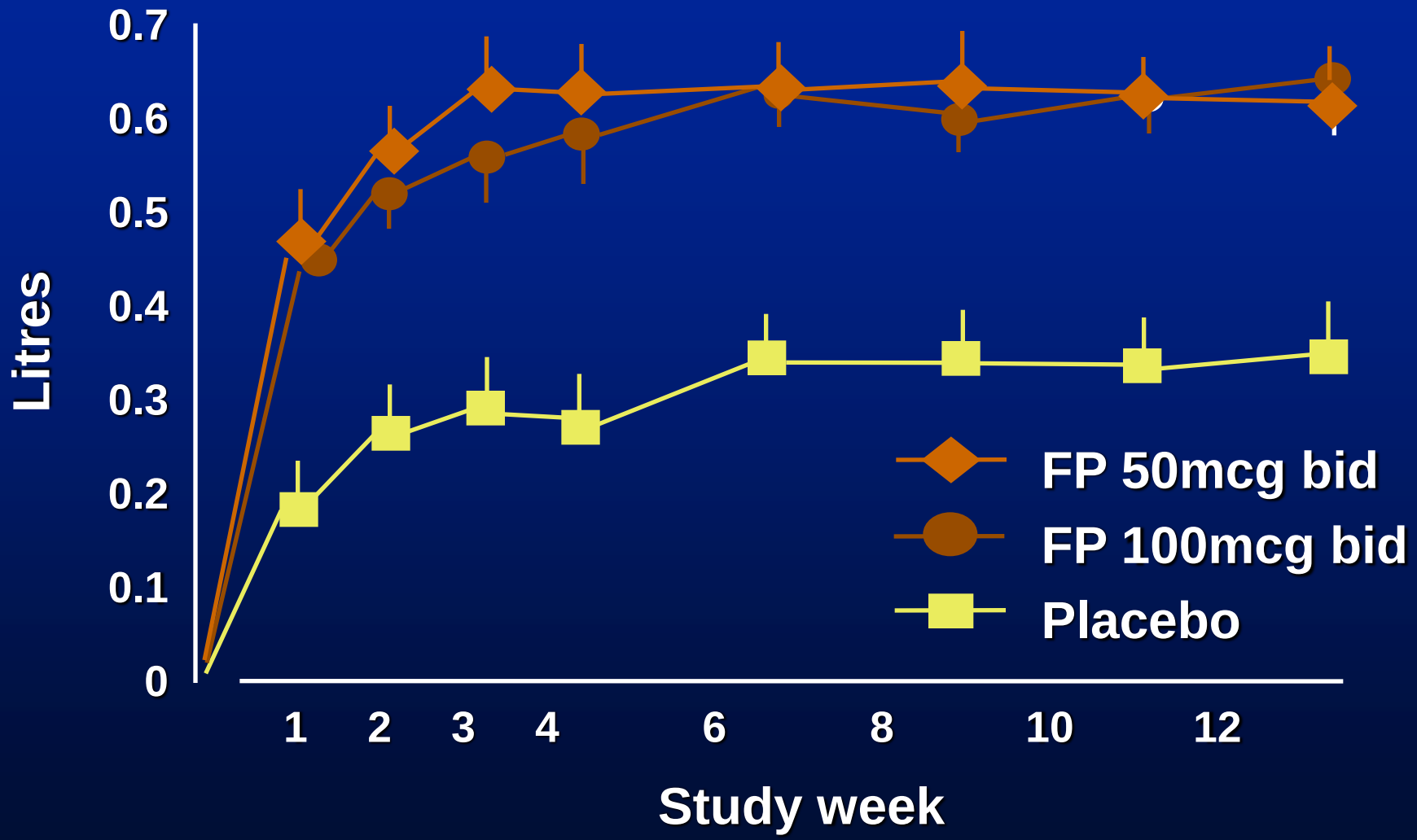


William Gillespie, Ph.D., 16 Aug 1996

Clinical Studies

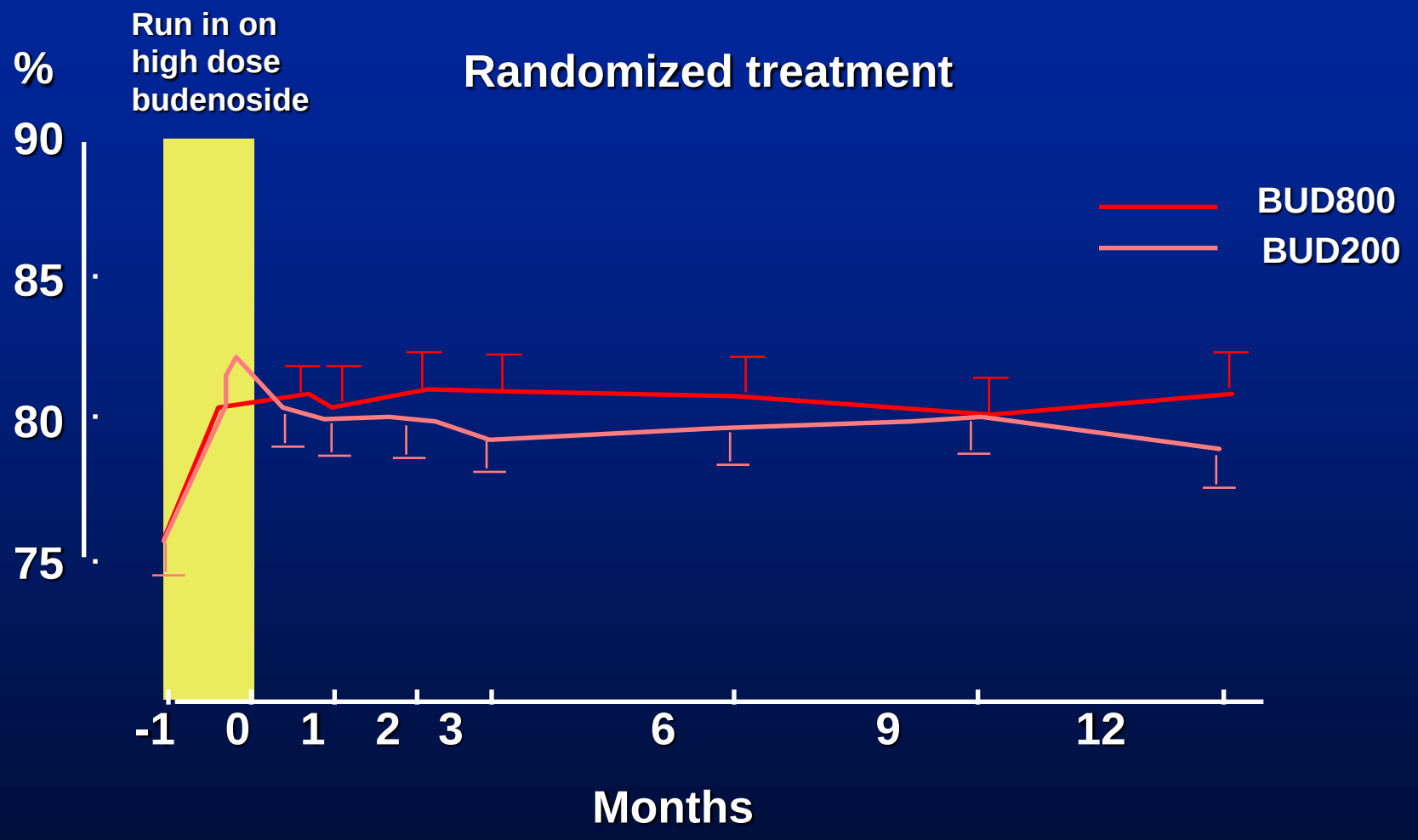
- **Pulmonary Function (FEV_1)**
- **Exhaled NO**

Mean change in FEV1



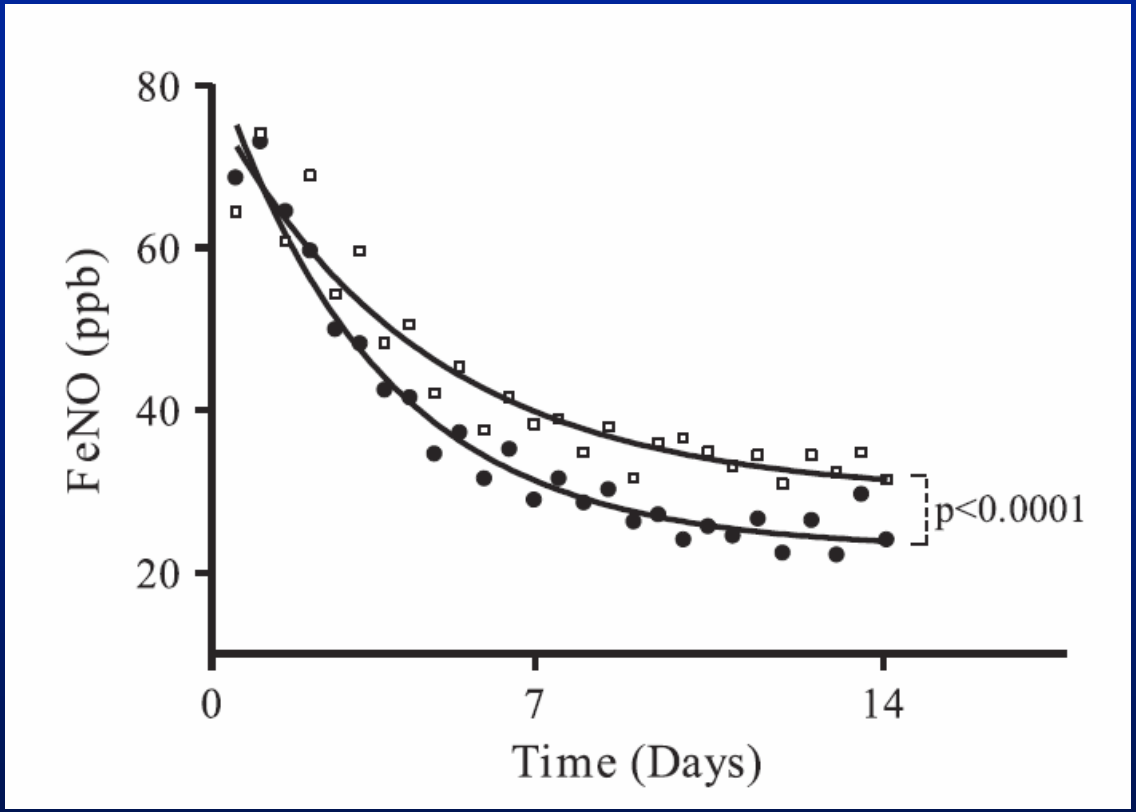
Larsen et al, 1994

FEV_1 as % of predicted value



Pauwels et al, 1997

Exhaled NO



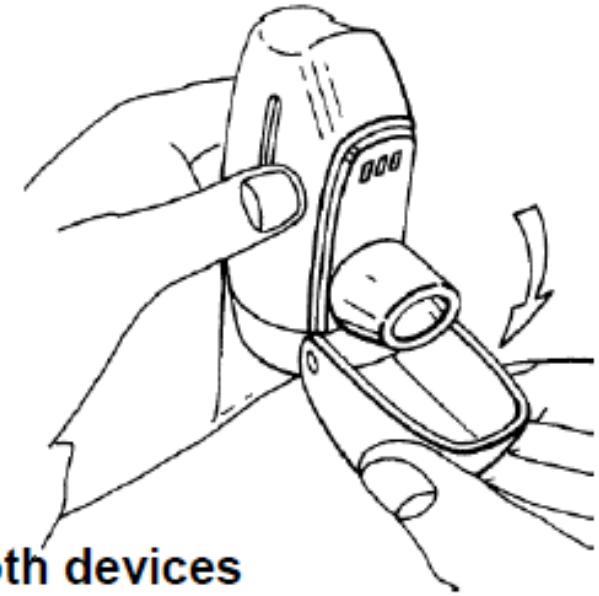
Time-series morning and evening fractional exhaled NO (FeNO) values after inhalation of either 100 (50 mcg bid) or 500 (250 mcg bid) mcg fluticasone propionate.

Anderson, W.J., P.M. Short, P.A. Williamson, and B.J. Lipworth, .Chest, 2012. 142(6): p. 1553-61.

Two Dry Powder Inhalers

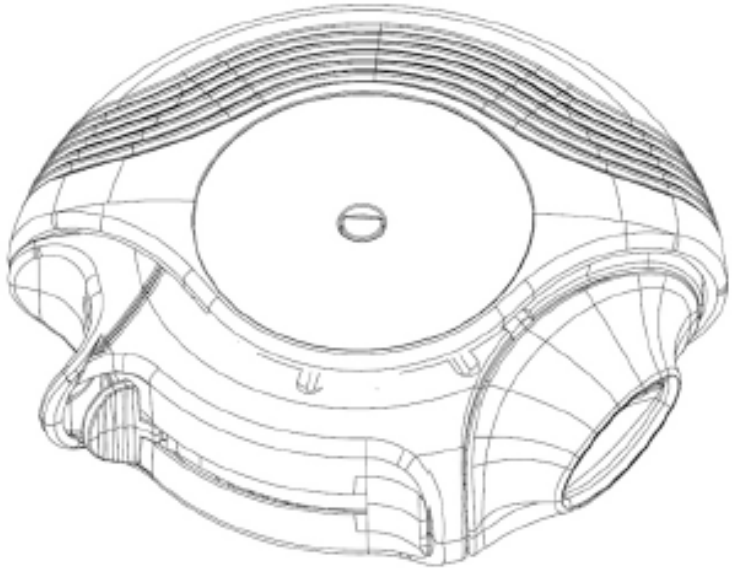
RPID

Multiple dose dry powder inhaler, containing a reservoir drug lactose blend from which unit doses are metered.



DISKUS

Multiple dose dry powder inhaler, containing unit doses of drug lactose blend in a peelable foil strip.



Both devices

Carrier: Lactose mono hydrate.

API / strength: micronised salmeterol 50 mcg and fluticasone propionate 250mcg.

Unit dose weight: 13mg.

Airflow resistance: 2.5KPa @ 60 L/min.

Perfomance: similar for range of flow rates.

Similar polymer composition.

RPID salmeterol/fluticasone propionate development

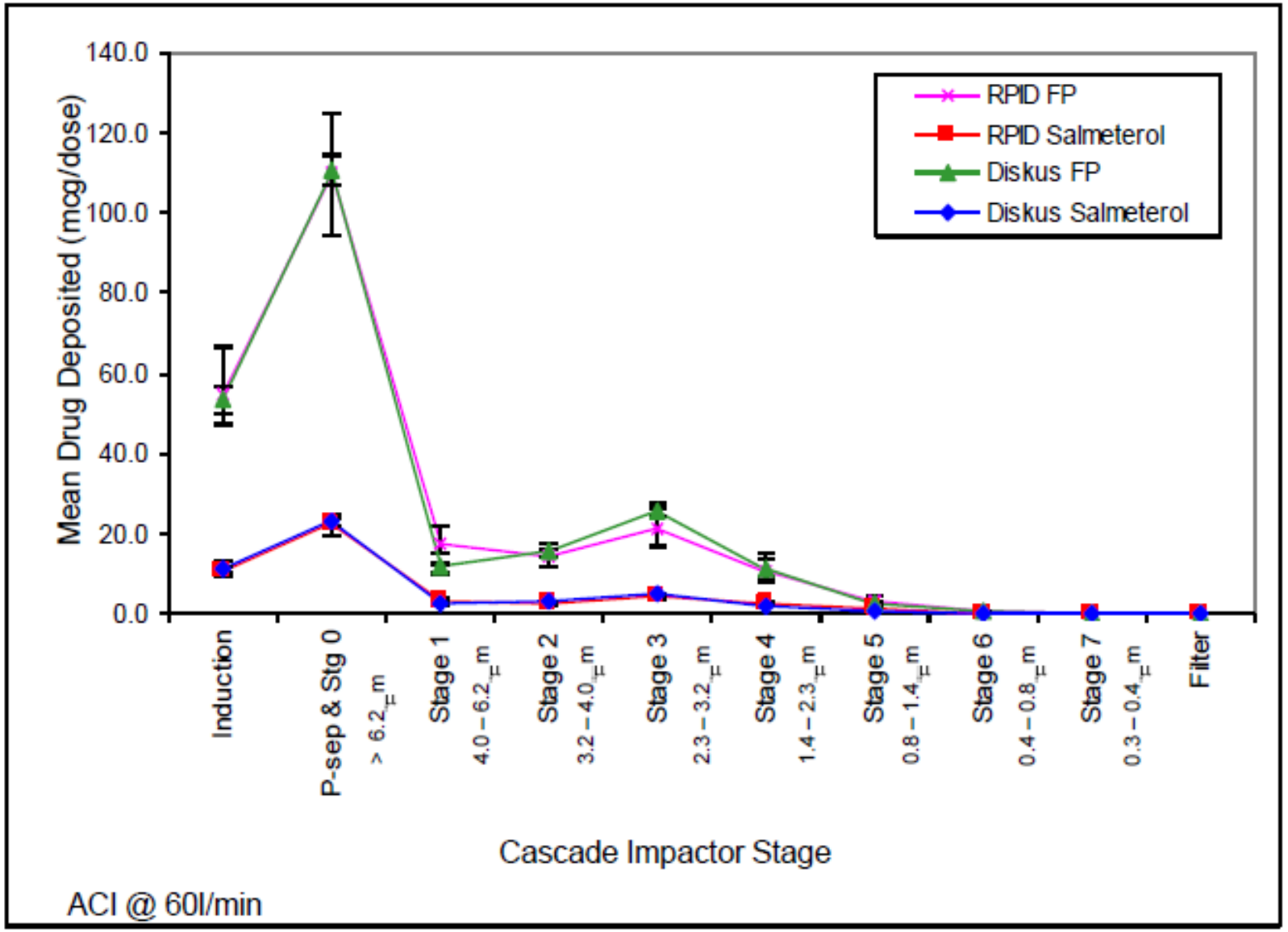
1. *In-vitro* assessment of emitted fine particle mass profiles by ACI for RPID versus Diskus.

2. Pharmacokinetic/pharmacodynamic study in adult asthmatics to determine *in vivo* drug delivery & systemic exposure for RPID versus Diskus.

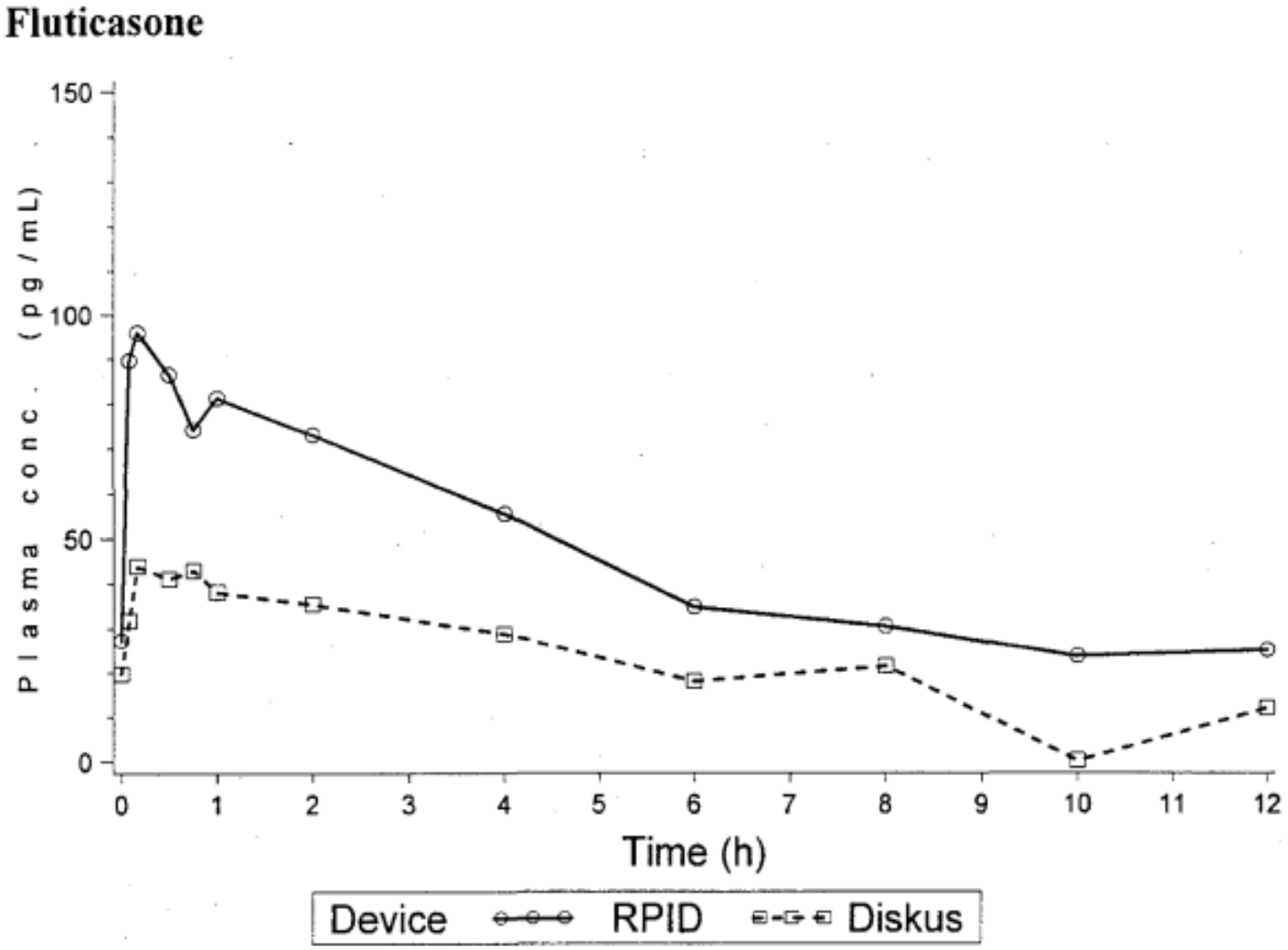
3. Clinical efficacy/safety studies in adult, adolescent and paediatric asthmatics to assess clinical equivalence.

Daley-Yates et al, Clinical Therapeutics, vol 31, Number 2, 370–385, 2009.

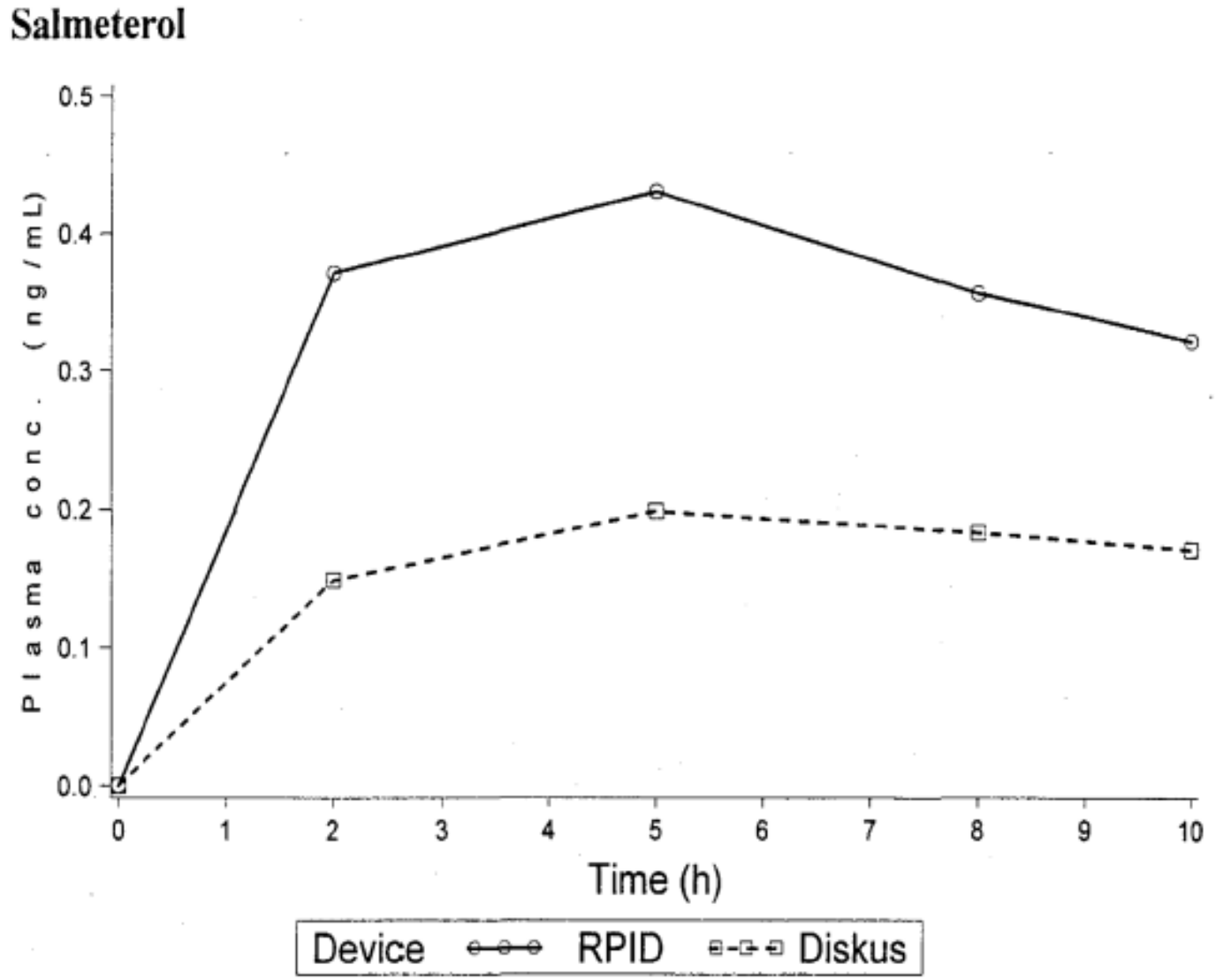
In-Vitro Test - RPID /Diskus ACI Profile



Results fluticasone propionate PK

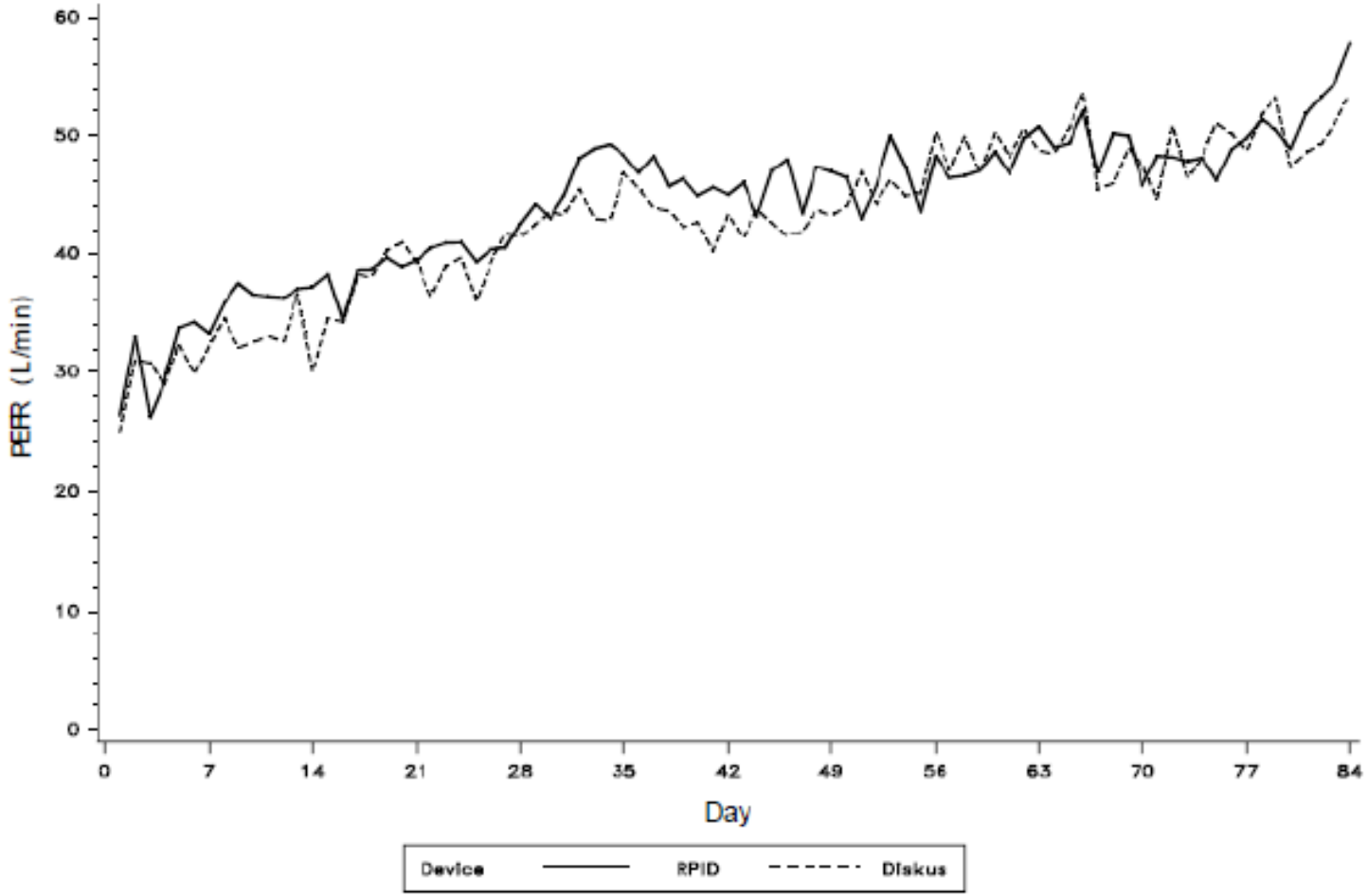


Results salmeterol PK



Change in mean morning PEFR wks 1-12

FP/SALM (250/50) via RPID and Diskus in children 4-14yrs



Conclusions

- Based on *in vitro* particle size profiling and clinical efficacy endpoints the two inhalers were deemed equivalent.

- Based on PK data the two inhalers were not equivalent.
  - There was a surprising and unpredictable lack of correlation between *in vitro* particle size profiles, *in vivo* drug delivery and systemic exposure.

- For this example, there was no evidence that PK data were a suitable surrogate to assess the bioequivalence of a topically acting orally inhaled drugs.

- PK data still have a role in evaluating systemic safety and *in vivo* inhaler performance.

Bioequivalence Assessment of Fluticasone Propionate / Salmeterol Xinafoate Dry Powder Inhalers (FDA 2013)

In Vitro Studies

- Single actuation dose content (SAC)
- Aerodynamic particle size distribution (APSD)

Pharmacokinetic (PK) BE Study

- All strengths, single-dose, two-way crossover
- Normal healthy males and non-pregnant females
- 90% CI within 80-125% of Reference

Bioequivalence Assessment of Fluticasone Propionate / Salmeterol Xinafoate Dry Powder Inhalers (FDA 2013)

Clinical Endpoint Study

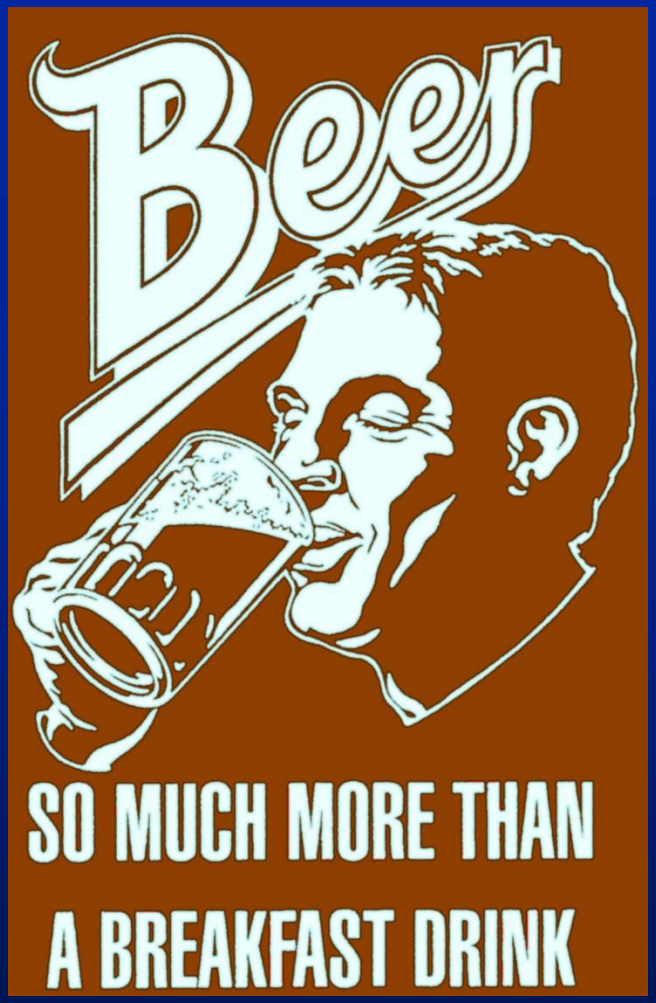
- Lowest strength only
- Randomized, multiple-dose, placebo-controlled, parallel group design with 2 week run-in followed by a 4-week treatment period of Placebo, Test (T) or Reference (R)
- Dose: 100/50 (FP/SX), twice daily
- Males & non-pregnant females with asthma ≥75% compliance
- T & R statistically significantly superior to placebo

Bioequivalence Assessment of Fluticasone Propionate / Salmeterol Xinafoate Dry Powder Inhalers (FDA 2013)

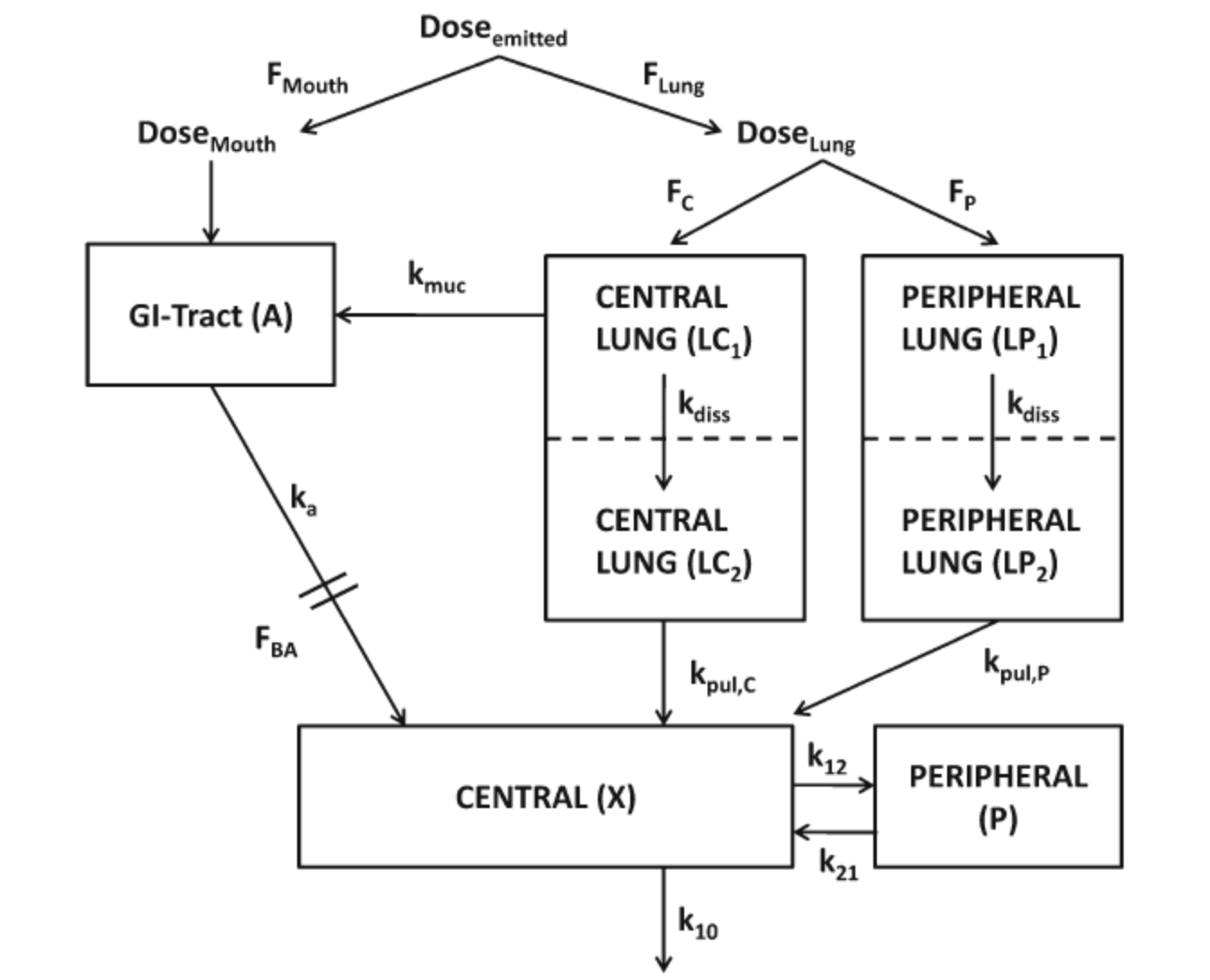
Clinical Study Endpoints

- $AUC_{0\text{-}12h}$ for serial FEV_1 on the first day (10 time points)
- FEV_1 measured in the morning prior to dosing on the last day of a 4-week treatment
- Baseline adjusted (change from pre-dose FEV_1)
- 90% CIs for the T/R ratios within 80-125%

Pharmacokinetics – So much more than just for Systemic Safety

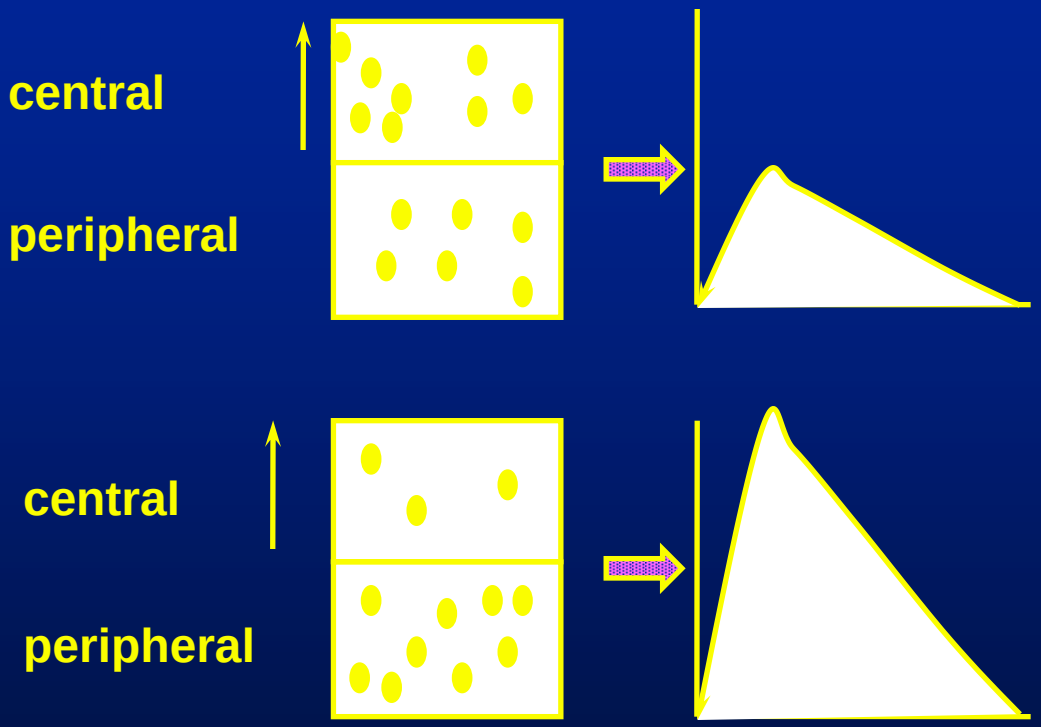


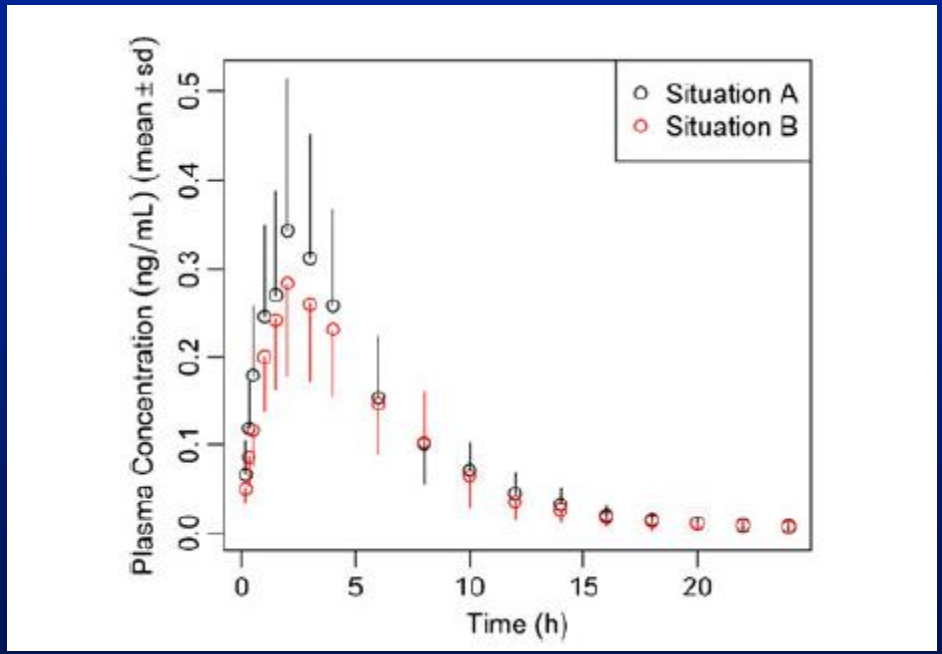
Pharmacokinetics – So much more than just for Systemic Safety



Weber & Hochhaus, AAPS J. 15:159 (2012)

Effect of C/P-Deposition Ratio on PK





Weber & Hochhaus, AAPS J. 15:159 (2012)

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**

Hochhaus (2012)

EMA PK Working Party March 2015

21. Evaluation of orally inhaled medicinal products: NEW

1. The extent to which plasma levels reflect bio-availability in the lung

PKWP Response:

In the EU, PK bioequivalence studies are considered an acceptable methodology to compare the lung deposition of two inhalation products containing the same active substance. In cases where the oral bioavailability of swallowed drug is negligible, or in case it is made negligible by active charcoal blockade, the plasma concentration time curve reflects both the extent of and the pattern of deposition within the lungs.

To conclude equivalent efficacy, both the amount of drug reaching the lungs and the deposition pattern of drug particles within the lung needs to be equivalent.

The area under the plasma concentration-time curve (or AUC) reflects the amount of drug that has reached the lungs. As the rate of absorption from the inhaled particles is different at different areas of the lung, the deposition pattern within the lung is mirrored by the shape of the plasma concentration-time curve during the absorption phase, i.e.Cmax and tmax.

In the case where intestinal absorption is not prevented, i.e. in a study without charcoal blockade, and thus absorption is the sum of the absorption via the lungs and intestinal absorption, as for other modes of administration, equivalent systemic safety can be concluded if two products give rise to equivalent systemic exposure (AUC and Cmax).

Pharmacokinetic endpoints may be more discriminative than PD or clinical endpoints, in particular the efficacy endpoints available for inhaled corticosteroids.

Widening of the acceptance range

Widening of the conventional 20% acceptance range based on high variability is only possible for Cmax according to the CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) (up to 69.84 – 143.19%) if a replicate design is conducted.

To support safety, it should be demonstrated that the systemic exposure is not higher for the test product than for the reference product, i.e. the upper limit of the 90% confidence interval should not exceed the upper bioequivalence acceptance limit 125.00.

Between-batch variability of the reference product and intra-batch variability over time

Variability in particle-size distribution between batches of the reference product or within a single batch of a reference product through their storage period can be significant. There may even be situations where it may be difficult to demonstrate PK bioequivalence between batches of the same reference product. Therefore, before the in vivo comparison, several batches of both test and reference products could be tested to identify representative batches (within ±15% of the corresponding median fine particle dose (or APSD)) of test and reference, respectively. In case of fixed combinations this may imply, if pre-specified in the protocol, the use of different batches for each component.

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.

Another approach that might be acceptable is to show that the side batches (batches in the tails of the distribution) representing the test product specifications are not superior and not inferior to the side batches of the reference product obtained from the market.

Proposal

- Pharmaceutical Properties equivalent (goalposts to be established)
- Systemic PK equivalent (charcoal if oral absorption)
- Cortisol and Growth Studies not needed
- Clinical Studies not sensitive enough and not needed

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