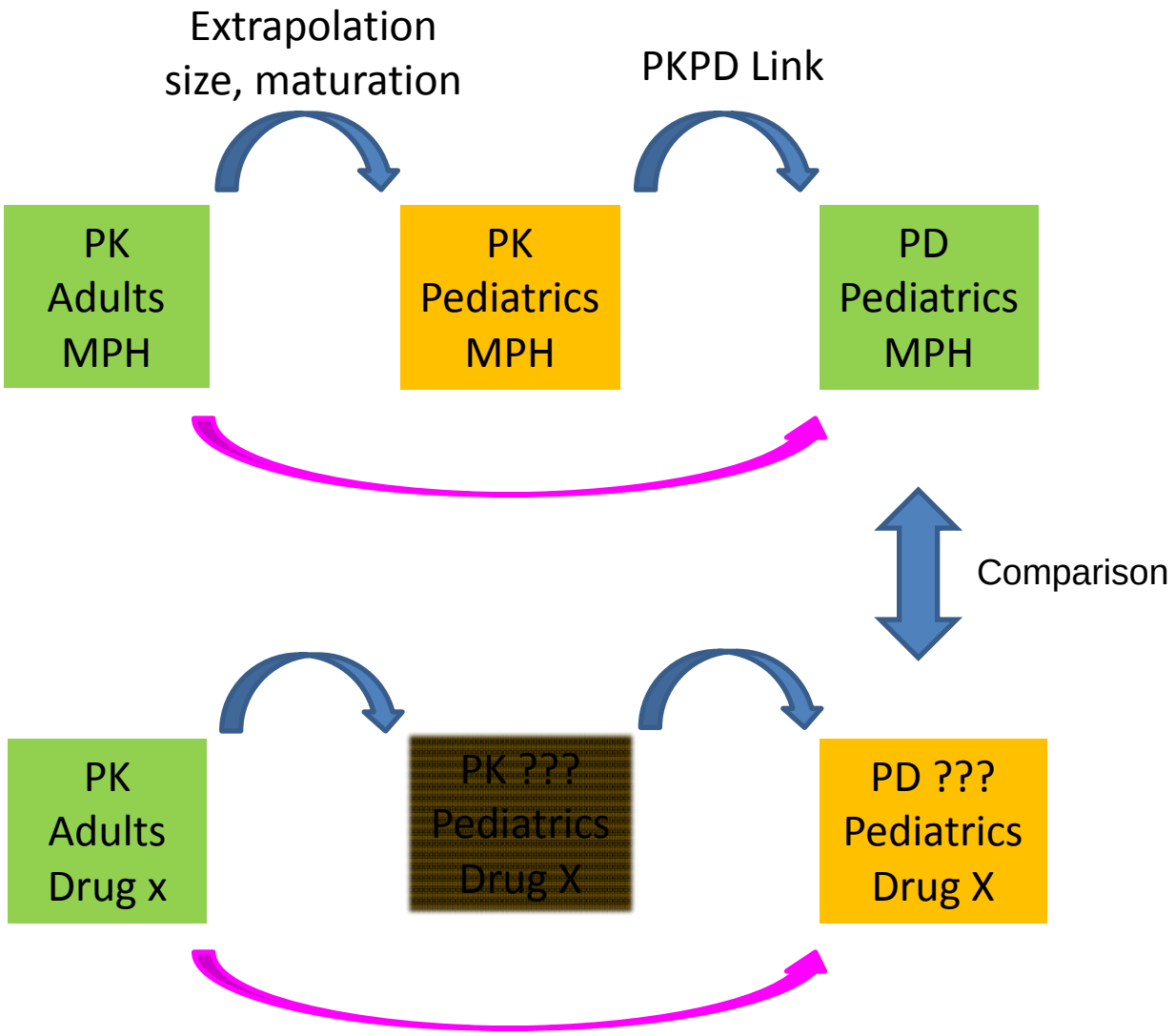
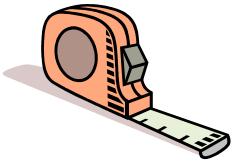
Background

- Methylphenidate (MPH) is a drug with a short duration of effect used in the treatment of ADHD in children, adolescents, and adults
- Extended-release (ER) products with different release profiles over the dose interval have been developed to eliminate the need for dosing during the school or working day
- Concerta® is *controlled*-release formulation

Objective





Clinical Measures of ADHD

- SKAMP-Composite
  - A composite score from the Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale
  - SKAMP-deportment & SKAMP-attention components
  - A validated classroom assessment tool used to evaluate the behavioral symptoms of ADHD in children in repeated fashion over a specified period of time
  - Smaller SKAMP-Composite scores indicate behavioral improvement

- PERMP
  - PERManent Product measures
  - PERMP-Attempted: quantifies the rate of behavior within a defined period of time (accurate measure of productivity)
  - PERMP-Correct: measures the *ability to learn* how to do math problems (not a precise measure)

A Daily Schedule During Laboratory Classroom Day

Study Hour*	Preparation	−0.75	0 (Dose)	1.5	3.0	4.5	6.0	7.5	9	12
Time		[6:45 AM]	[7:30 AM]	[9:00 AM]	[10:30 AM]	[12:00 PM]	[1:30 PM]	[3:00 PM]	[4:30 PM]	[7:30 PM]
Vital signs†		X		X	X	X	X	X	X	X
SKAMP deportment			X	X	X	X	X	X		X
SKAMP attention			X	X	X	X	X	X		X
PERMP			X	X	X	X	X	X		X
Complete Barkley Scale (parent/ guardian)	X									
Assess AEs	X									

- A good well-controlled study setting
- 7 scores per study day
- Measurements at the same clock times per study day
  - Every 1.5 hours from 7:30 am
  - Sampling time error interval ± 15 minutes

Johnson & Johnson PHARMACEUTICAL RESEARCH & DEVELOPMENT, L.L.C.

Swanson *et al.* Pediatrics, 113:e206, 2004

Challenges in Model Building

- Combination of summary data from literature and individual data from J&J studies
  - Model-based meta-analysis
- Lack of trials with simultaneous PK and PD data collection
  - PK from adult
  - PD from pediatrics
- Lack of a disease progress model
  - To separate true drug effect from observed combined placebo & drug effects
- Various study designs
  - Titration to a desired effect in each subject, and administration of the individual optimal dose during the assessment days in some studies
  - Different treatments between assessment days

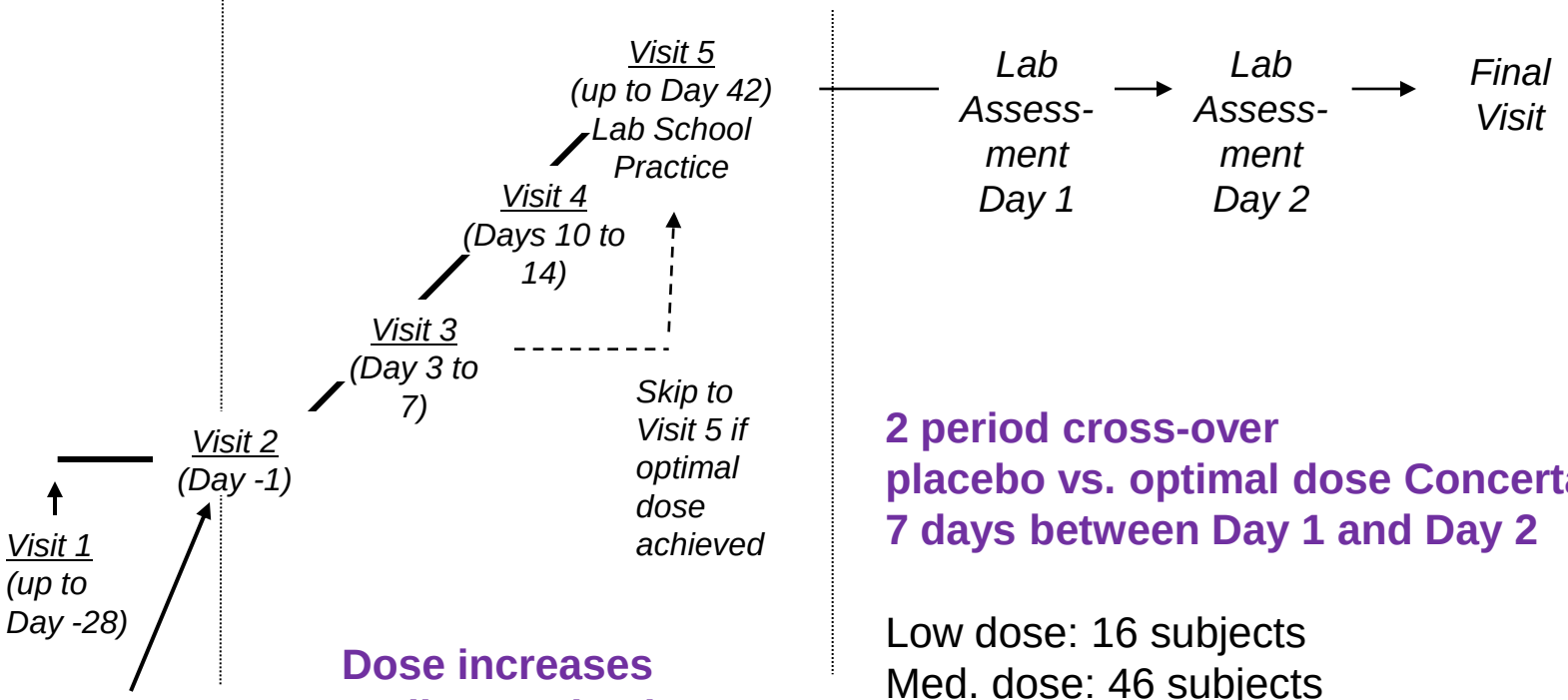
Individualized Dose I

An ADHD Study Design: Laboratory School (Study ABC)

Screening/ Washout Phase
(up to 28 days)

Open-Label Dose Adjustment Period
(1 to 6 weeks)

Double-Blind Assessment Period
(up to 6 weeks)



Dose increases until an optimal dose is achieved

2 period cross-over
placebo vs. optimal dose Concerta®
7 days between Day 1 and Day 2

Low dose: 16 subjects
Med. dose: 46 subjects
High dose: 77 subjects

Individualized Dose II

An ADHD Study Design: Laboratory School (COMACS Study)

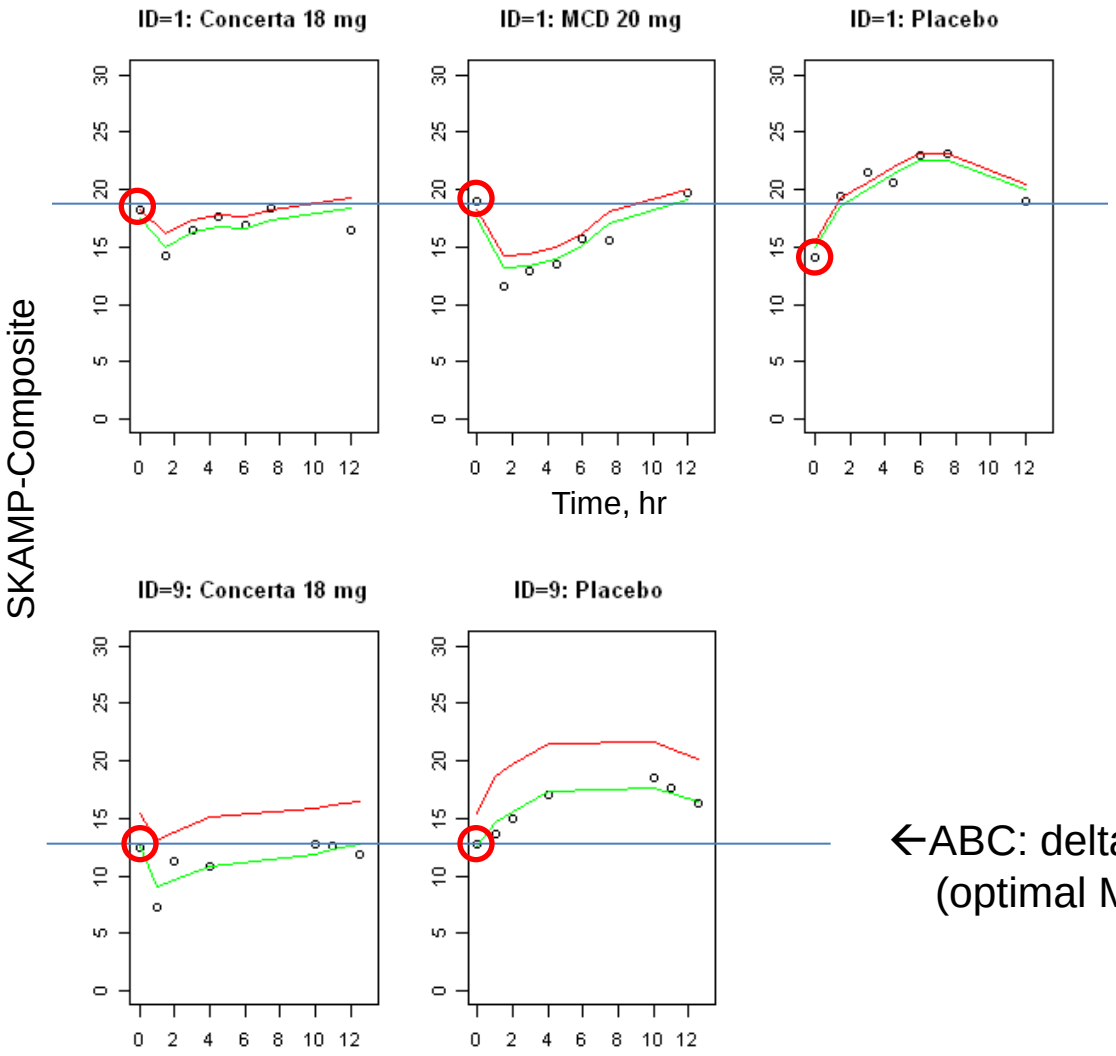
TABLE 1. Dosage Stratification

Previous MPH Daily Dose	Stratification Dose
Low dose ≤15 mg of IR MPH or ≤20 mg of ER MPH (eg, 5 mg BID/TID or 20 mg of MPH SR)	MCD 20 mg vs CON 18 mg vs PLA (dose level 1)
Medium dose >10 to ≤30 mg IR MPH or >20 to ≤40 mg of ER MPH (eg, 10 mg BID/TID or 40 mg of MPH SR)	MCD 40 mg vs CON 36 mg vs PLA (dose level 2)
High dose >30 mg IR MPH or >40 mg of ER MPH (to a maximum of 60 mg) (eg, 15 mg BID/TID or 60 mg of MPH SR)	MCD 60 mg vs CON 54 mg vs PLA (dose level 3)

- Subjects assigned to the dose closest to their previous dose & remained at the level for the study duration
- 3-way cross-over: placebo, Concerta®, Metadate CD®
- 7 days in each treatment: assessment on the 7th days
- No wash-out period
- 184 subjects

Swanson *et al.* Pediatrics, 113:e206, 2004

Baseline is Different Depending on Treatment History



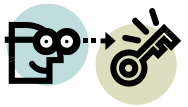
←COMACS: delta needed
(7th day assessment)

←ABC: delta not needed
(optimal MPH given between study visits)

Design Dependent Parameter: delta

Other Study Designs

Treatment	Design	Data	N
d-MPH 20 mg/ Placebo	Patients were stabilized on Concerta 36-54 or d-MPH[a] 20-30. Then, 7 days of 20 mg d-MPH or placebo with assessment on the last of seven days. 2 period cross-over	SKAMP-Composite; PERMP-Attempted and PERMP-Correct **change from baseline** at 0, 0.5, 1, 2, 4, 6, 8 hrs	86
Concerta 36 mg/ Concerta 54 mg/ d-MPH 20 mg/ d-MPH 30 mg/ Placebo	Patients were stabilized on Concerta 36-54 or d-MPH[a] 20-30 mg/day. Then, 5 treatment period cross-over with assessments on day 7 of each period.	SKAMP-Composite, PERMP-Attempted and PERMP-Correct **change from baseline** at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 11, 12 hrs	84
Ritalin LA 20 mg/ Concerta 18 mg/ Concerta 36 mg/ Placebo	Patients were stabilized on 10 mg BID MPH and remained on this medication during the study except for 4 assessment days when they were administered randomized treatments. There was a washout day without medication before each assessment. 4 period cross-over.	SKAMP–Composite, PERMP –Attempted, and PERMP-Correct at 0, 0.5, 1, 2 ,3 ,4, 6, 8 hrs can be derived from the presented data	36
d-MPH 20 mg/ d-MPH 30 mg/ Concerta 36 mg/ Concerta 54 mg/ Placebo	Patients were stabilized on Concerta 36-54 or d-MPH[a] 20-30 mg/day. Then, 5 treatments 7 days each, assessments on day 7 of each treatment. 4 period cross-over	SKAMP–Composite, PERMP –Attempted, and PERMP-Correct **change from baseline** at 0, 0.5, 1, 2, 3, 5, 7, 9, 10, 11, 12 hrs	82
d-MPH 20 mg/ Placebo	Patients were stabilized on MPH 20–40 mg/day. Then, 5 days of randomized treatment, then 1 day washout, then assigned treatment and assessments. 2 period cross-over	SKAMP–Composite, PERMP –Attempted, and PERMP-Correct at 0, 1, 2, 4, 6, 8, 9, 10, 11, 12 hrs can be derived from the presented data	54



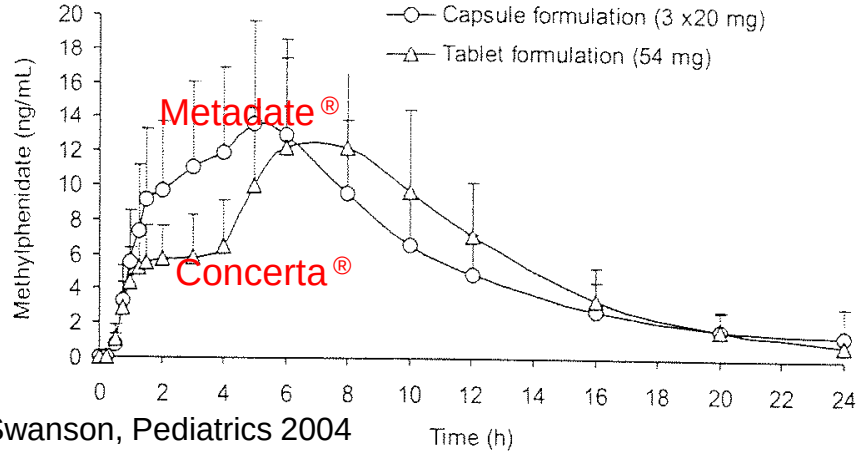
PK & PD Data Used

- Four different PK profile formulations
  - Concerta®, Metadate CD®, Focalin XR®(d-MPH), Ritalin LA®
- Nine PD study
  - 8 studies for model building
  - 1 study for external evaluation

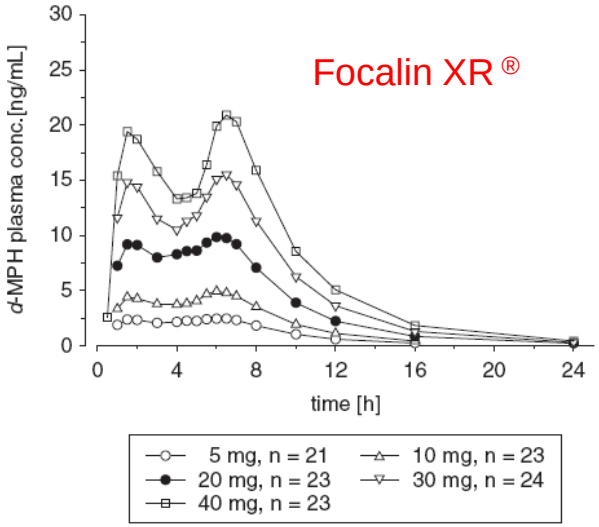
ID	PD type	Source of Data		Available Treatments / Dose Levels				
		PK	PD	Placebo	Concerta	MCD	dMPH[a]	Ritalin LA
1	raw score	PK1, PK6	PD3	0	18	20		
2	raw score	PK1, PK6	PD3	0	36	40		
3	raw score	PK6	PD3	0	54	60		
4	change from baseline	PK4	PD4	0			20	
5	change from baseline	PK4, PK6	PD5	0	36, 54		20, 30	
6	raw score	PK1, PK2	PD6	0	18, 36			20
7	change from baseline	PK4, PK6	PD7	0	36, 54		20, 30	
8	raw score	PK4	PD8	0			20	
9	raw score	PK1	ABC	0	18			
10	raw score	PK1	ABC	0	36			
11	raw score	PK6	ABC	0	54			

No PK Model Building

- The PK model of each formulation was not built
- The published mean PK data were used as a driver in the PD model



Swanson, Pediatrics 2004



Tuerck JCP 2007

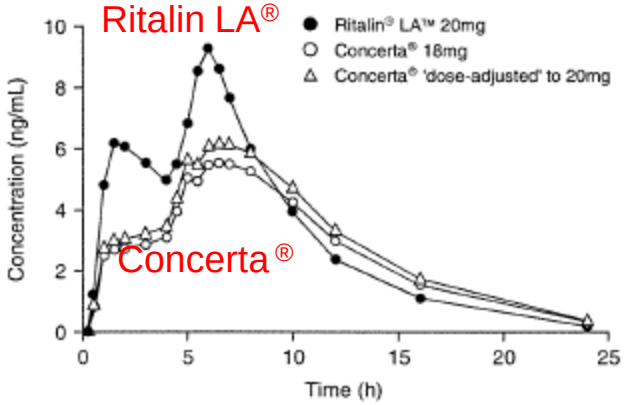


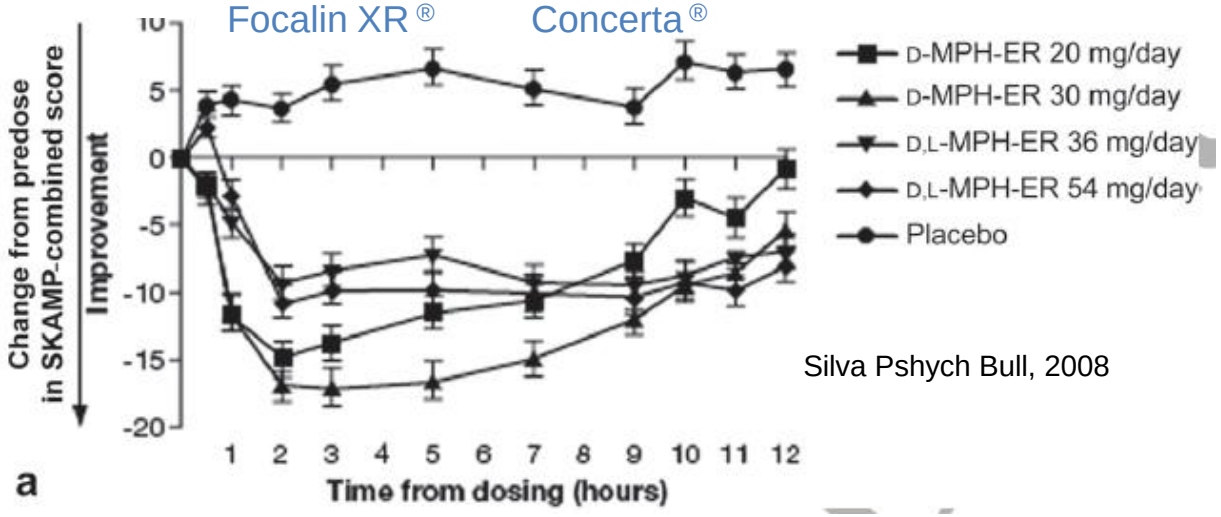
Fig. 1. Ritalin® LA™ 20mg versus Concerta® 18mg concentration versus time profile (reproduced from Markowitz et al.,[11] with permission).

Lopez, Pediatric Drugs 2003

DP – *PK* – PD modeling!

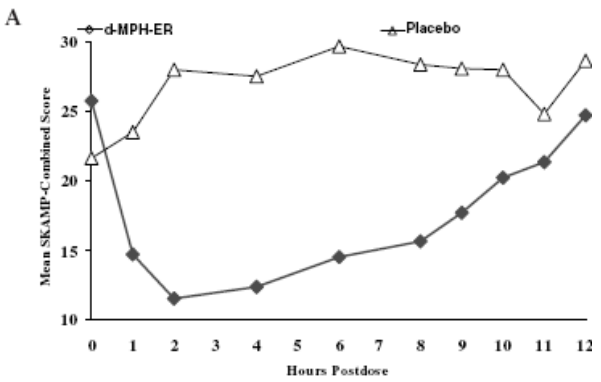
Some of the SKAMP Data Used

Focalin XR ® Concerta ®



Silva Pshych Bull, 2008

Focalin XR ®



Silva, J Child Adol Psych, 2006

Ritalin LA®
Concerta ®

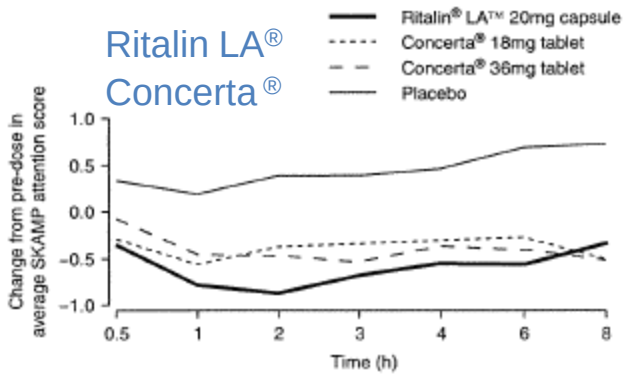
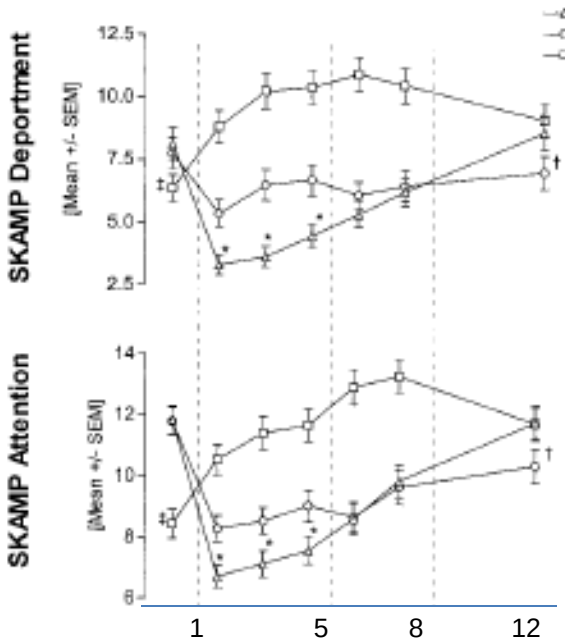


Fig. 3. Plot of average SKAMP-attention score over time: change from pre-dose rating. **SKAMP** = Swanson, Kotkin, Agler, M-Flynn and Pelham rating scale.

Lopez, Pediatric Drugs 2003

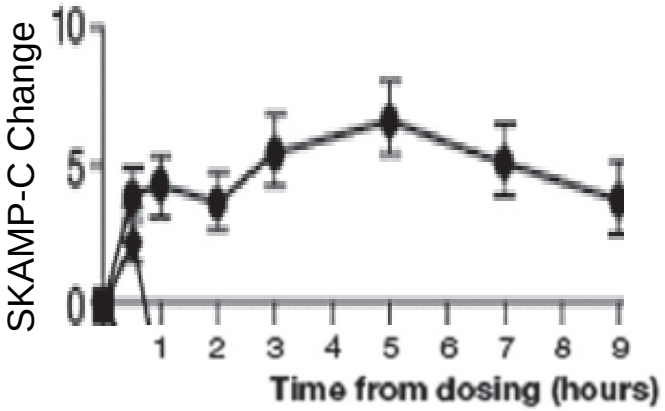


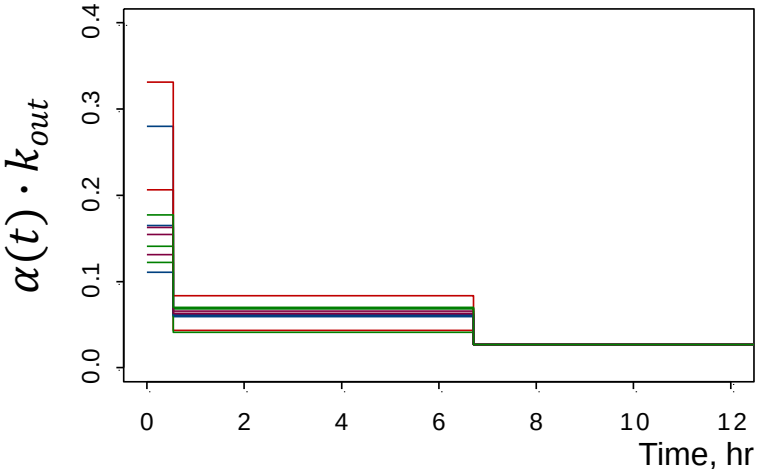
Metadate ®
Concerta ®

Swanson, Pediatrics 2004

Note placebo effect / disease progression!

Disease Progress (Placebo) Model





- Disease progress was described from the placebo data
- Inversed indirect response model with time varying coefficient

$$\frac{dB}{dt} = k_{in} - \alpha(t) \cdot k_{out} \cdot B$$

$$at\ S.S, B_0 = {}^{k_{in}}/_{k_{out}}$$

$$\frac{d(\frac{B}{B_0})}{dt} = k_{out} - \alpha(t) \cdot k_{out} \cdot \frac{B}{B_0}$$

$$\frac{dA}{dt} = k_{out} \cdot \{1 - \alpha(t) \cdot A\} \qquad 0 < A \leq 1$$

$$placebo\ score = constant - B_0 \cdot A$$

Empirically, constant → B0

$$placebo\ score = B_0 \cdot (1 - A)$$

*PK-*PD Model

$$Effect = delta + \frac{E_{max} \cdot C}{EC_{50} + C} \qquad EC_{50} = EC_{50,start} \cdot \left(1 + \frac{E_t \cdot time^{\gamma}}{T_{50}{}^{\gamma} + time^{\gamma}}\right)$$

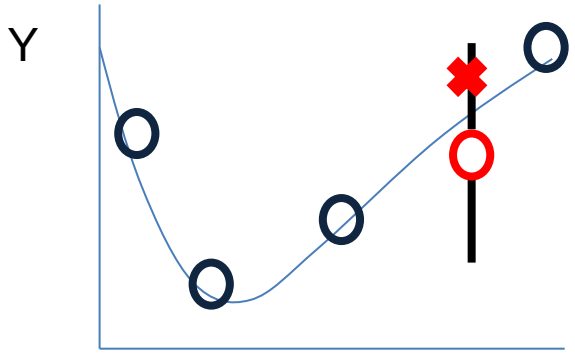
- A simple Emax-type model
- delta: The score difference at baseline depending on the treatment between assessment days
- Tolerance on EC50:
  - as time passes, higher EC50 → more drug is needed to achieve the same effect

Score(t) = Placebo(t) – Effect(t)

$$Y = Score(t) + \frac{1}{\sqrt{n_{ik}}}\varepsilon_{ik} \quad \text{or} \quad Y = Score(t) - Score_{Baseline} + \frac{\sqrt{2}}{\sqrt{n_{ik}}}\varepsilon_{ik}$$

- Available PD data: raw scores or change from the baseline

Weighting in Meta-Analysis



Study i, Arm k

Subject j

Individual score ✖ → $Y_{ij}(t) = score(t) + \eta_i^{study} + \eta_{ij}^{subject} + \varepsilon_{ij}(t)$

Each arm has a different number of subjects: n_{ik}

Mean score in an arm O → $\bar{Y}_{ik}(t) = \frac{1}{n_{ik}} \sum_{arm_{ik}} Y_{ij}(t)$

our observation!!

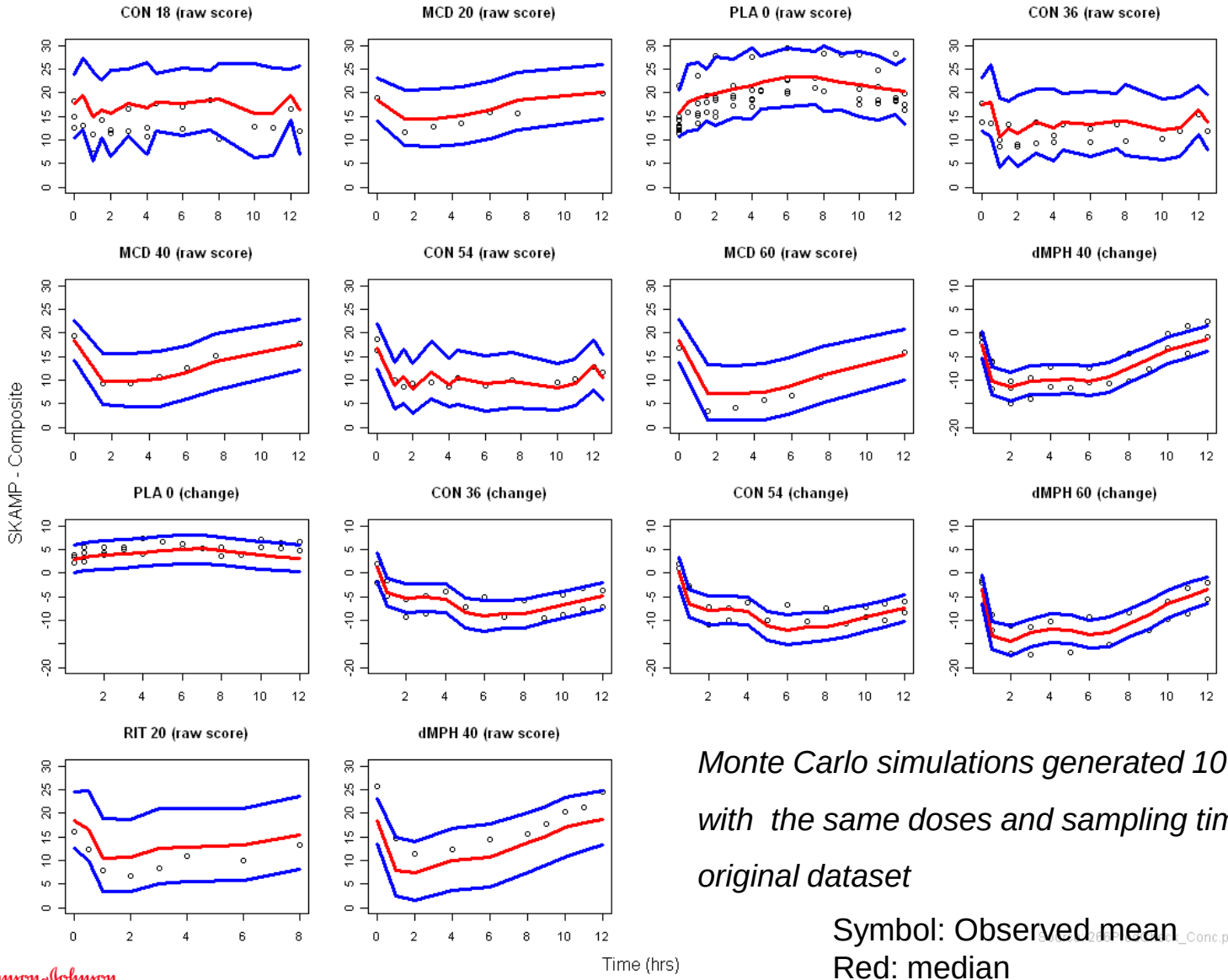
$$\approx score(t) + \eta_i^{study} + \frac{1}{\sqrt{n_{ik}}}\eta_{ik}^{arm} + \frac{1}{\sqrt{n_{ik}}}\delta_{ik}$$

Ahn & French, JPKPD 2010, 37:179-201

$$\eta_{ik}^{arm} = \frac{1}{\sqrt{n_{ik}}}\sum_{(ij)}\eta_{ij}^{patient} \quad \text{and} \quad \delta_{ik}(t) = \frac{1}{\sqrt{n_{ik}}}\sum_{(ij)}\varepsilon_{ij}(t)$$

$$\eta_{ik}^{arm} \sim N(0, \omega_p^2) \qquad \delta_{ik}(t) \sim N(0, \sigma^2)$$

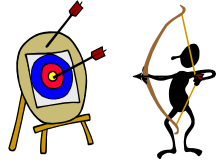
Internal Evaluation



Monte Carlo simulations generated 1000 datasets with the same doses and sampling times of the original dataset

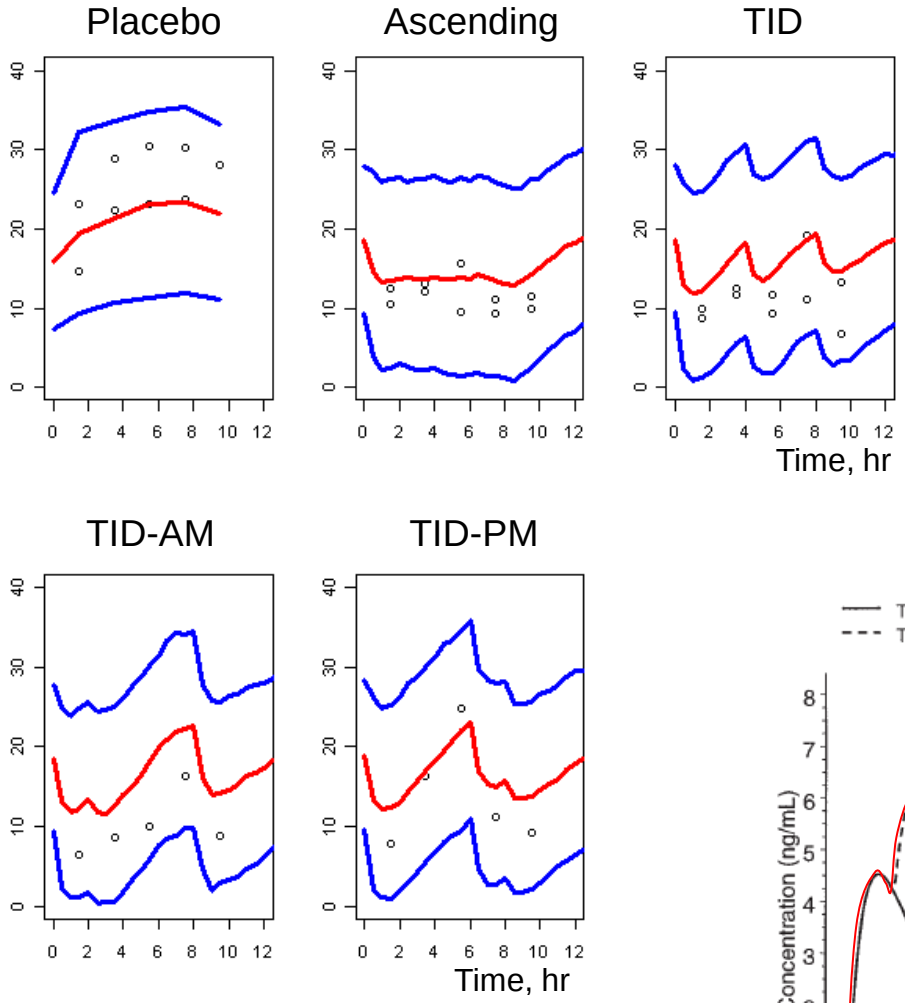
Symbol: Observed mean
Red: median
Blue: 90% interval of simulated scores

External Evaluation

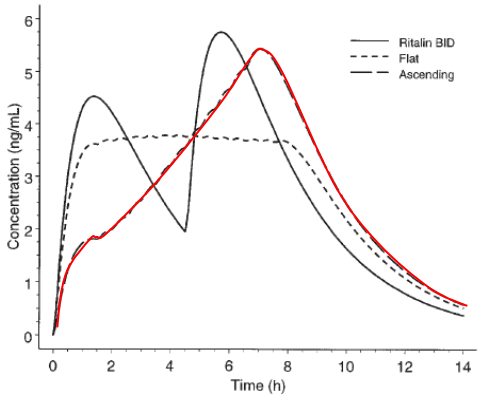


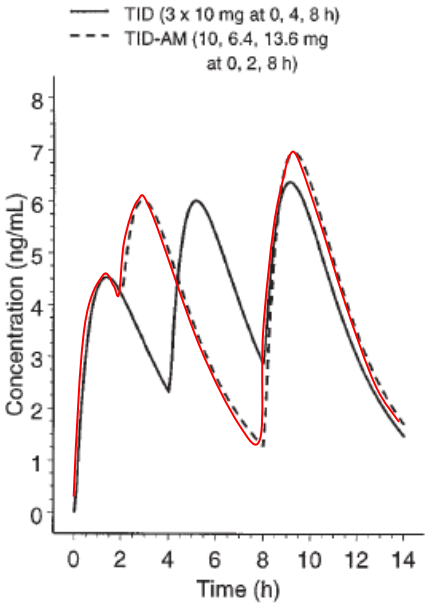
B_0 missing

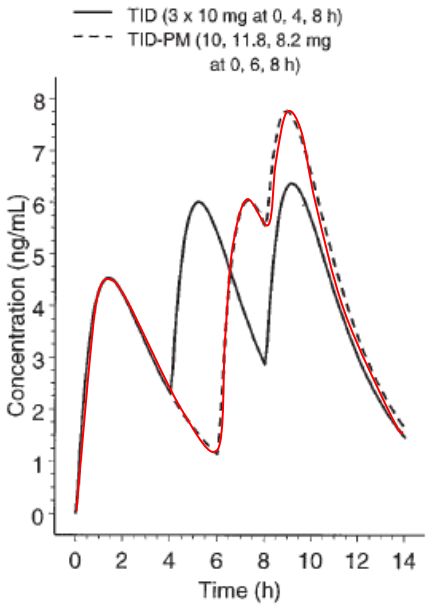
SKAMP-Composite



This study was not included in the model building







Red: median
Blue: 90% prediction interval
Symbol: observed mean

Closing Remarks

- The DP-*PK*-PD model allowed prediction of response in pediatrics with various PK profiles from adults
- Model-based meta-analysis is a useful tool to do “competitive landscaping” of compounds of interest
  - Go/no-Go decision
  - Decision of a study design (power calculation with n, study period, doses, etc.)

Data Sources

PK

- PK1: Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology April 13, 2010, BRIEFING INFORMATION Page 32
- PK2: Ritalin® LA label (file 21-284_Ritalin LA_prntlbl.pdf)
- PK4: Tuerck D, *et al*. Dose-proportional pharmacokinetics of d-threo-methylphenidate after a repeated-action release dosage form. J Clin Pharmacol. 2007 Jan;47(1):64-9.
- PK6: Gonzalez MA, *et al*. Methylphenidate bioavailability from two extended-release formulations,Int. J Clinical Pharmacology Therapeutics 2002 40 (4): 175-184.

PD

- PD1: Study ABC, J&J
- PD2 (Study 007, J&J): Swanson J, *et al*. Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children, Clin. Pharmacol. Ther. 1999 Sep; 66(3):295-305.
- PD3: Swanson JM, *et al*. COMACS Study Group. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). Pediatrics. 2004 Mar; 113(3 Pt 1):e206-16.
- PD4: Brams M, *et al*. A randomized, double-blind, crossover study of once-daily dexmethylphenidate in children with attention-deficit hyperactivity disorder: rapid onset of effect. : CNS Drugs. 2008;22(8):693-704.
- PD5: Muniz R, *et al*. Efficacy and safety of extended-release dexmethylphenidate compared with d,l-methylphenidate and placebo in the treatment of children with attention-deficit/hyperactivity disorder: a 12-hour laboratory classroom study. J Child Adolesc Psychopharmacol. 2008 Jun;18(3):248-56.
- PD6: Lopez F, *et al*. Comparative efficacy of two once daily methylphenidate formulations (Ritalin LA and Concerta) and placebo in children with attention deficit hyperactivity disorder across the school day. Paediatr Drugs. 2003;5(8):545-55.
- PD7: Silva R, *et al*. Treatment of Children with Attention-Deficit/Hyperactivity Disorder: Results of a Randomized, Multicenter, Double-Blind, Crossover Study of Extended-Release Dexmethylphenidate and d,l-Methylphenidate and Placebo in a Laboratory Classroom Setting. Psychopharmacol Bull. 2008;41(1):19-33.
- PD8: Silva RR, *et al*. Efficacy and duration of effect of extended-release dexmethylphenidate versus placebo in schoolchildren with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2006 Jun;16(3):239-51.
- PD9: Pelham WE, *et al*. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. Pediatrics. 2001 Jun;107(6):E105.


REDUCE
REUSE
RECYCLE