PharmacoMetrica

Drug-disease modeling approach to describe the relationship between long-acting methylphenidate exposure and clinical response

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Disclosure

Roberto Gomeni, PhD was consultant for: Ironshore Pharmaceuticals & Development, Inc., Sunovion Pharmaceuticals Inc., Supernus Pharmaceuticals, Inc., Teva Branded Pharmaceutical Products R&D, Inc., Biomedical Science Institutes, Singapore, Nanomi BV, The Netherlands, Laboratorios Liconsa, S.A., Spain, General Hospital Corporation, Boston, Massachusetts, and UCB Biopharma S.P.R.L.

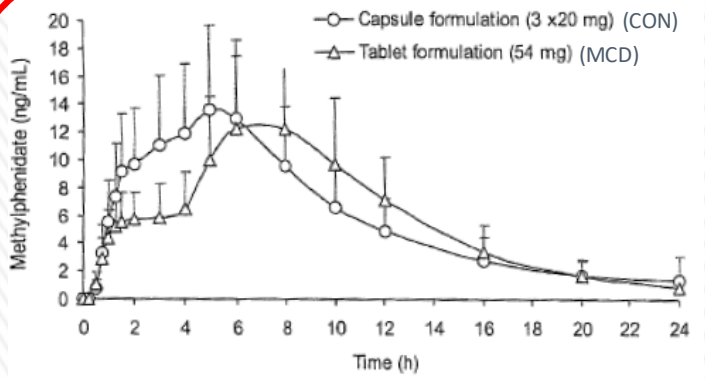
Outline

- Methylphenidate (MPH) is currently used to treat children with attention deficit hyperactivity disorder (ADHD).
- Several modified release formulations characterized by complex in-vivo drug release process have been developed in the attempt to improve the treatment efficacy.
- Model-based approach is recognized as a tool to make drug development more productive and to better support regulatory and therapeutic decisions.
- The objective of this presentation is to develop a model-based framework (i.e., a drug-disease model, and a response surface analysis) to identify the relevant factors affecting performances of MPH treatments and to use this modeling framework to evaluate the ideal properties of a MPH formulation appropriate for maximizing the clinical benefit of a treatment.

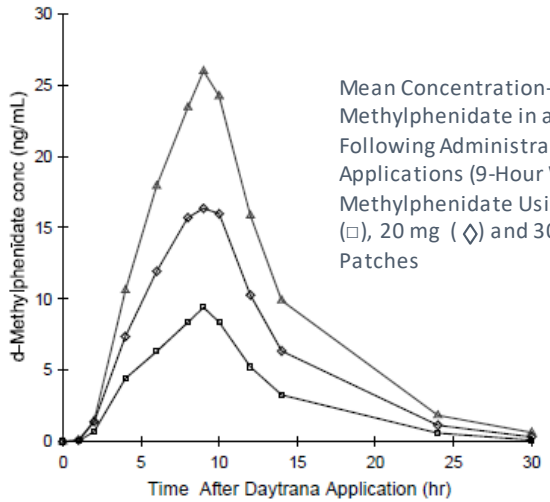
Question

Is the rate of absorption and the extent of exposure a determinant of the clinical response of a MPH treatment?

Exposure-Response



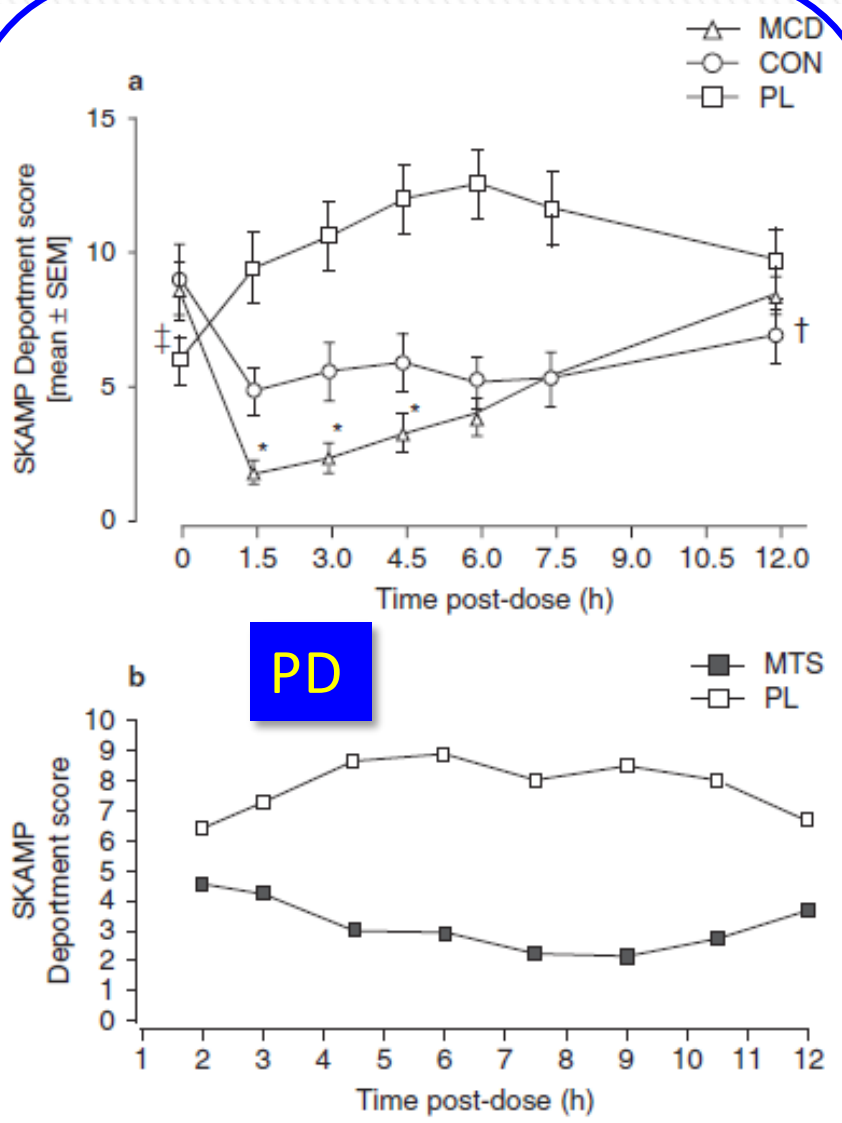
González, M.A., et al. Methylphenidate bioavailability from two extended-release formulations. Int. J. Clin. Pharmacol. Ther. 40, 175-84 (2002).



Mean Concentration-time Profiles for *d*-Methylphenidate in all Patients (N=34) Following Administration of Single Applications (9-Hour Wear Time) of *d,l*-Methylphenidate Using Daytrana 10 mg (□), 20 mg (◊) and 30 mg (Δ) per 9-Hour Patches

PK

Daytrana (methylphenidate transdermal system) film label - FDA https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021514s011lbl.pdf



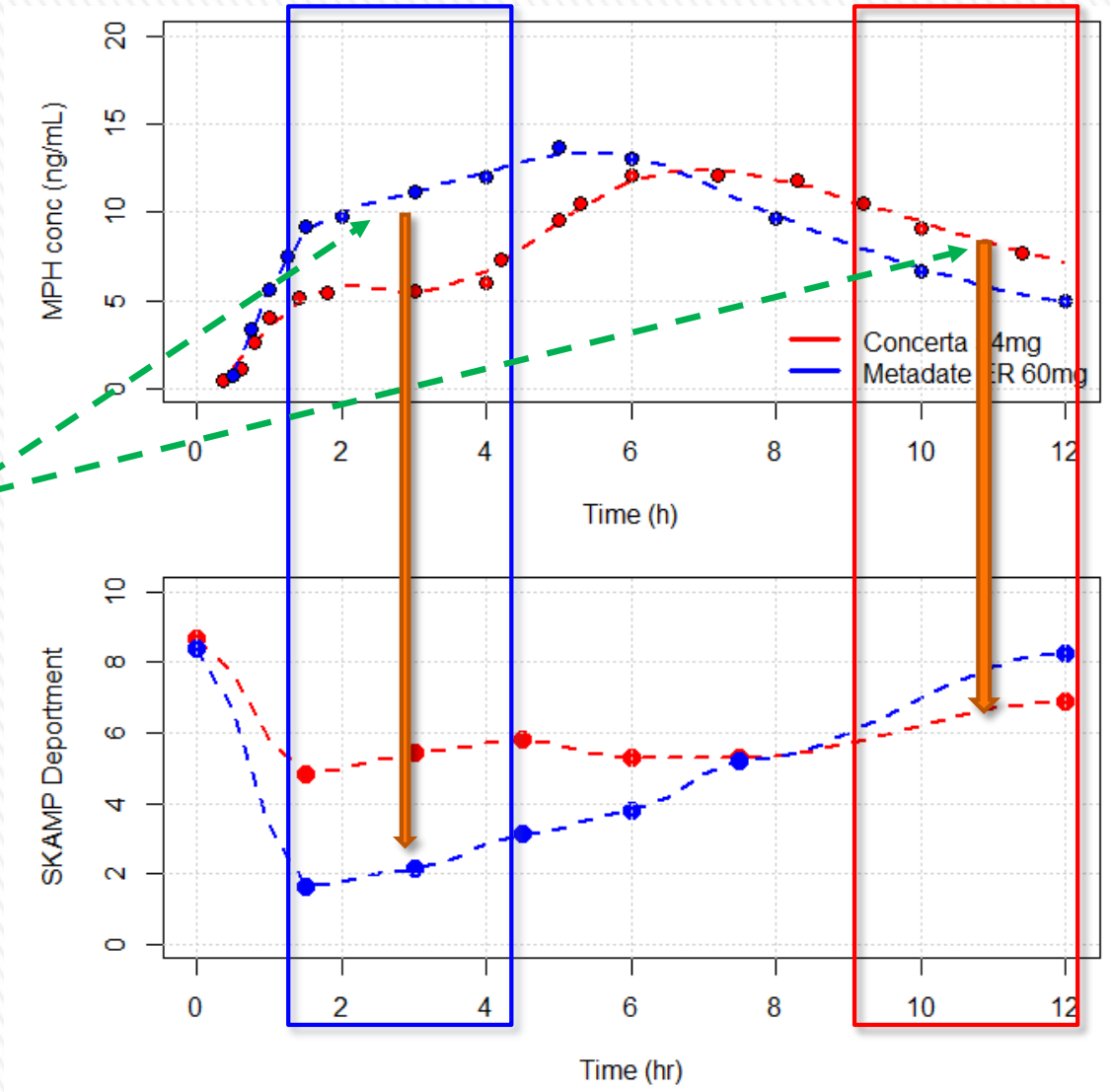
Wigal S.B. Efficacy and Safety Limitations of Attention-Deficit Hyperactivity Disorder Pharmacotherapy in Children and Adults. CNS Drugs 2009; 23 Suppl.1: 21-31

*Legend: **CON**=CONCERTA®, **MCD**=METADATE ER®, **MTS**=DAYTRANA®*

ER Oral Formulations: Treatment Effect

Higher exposure

Higher response

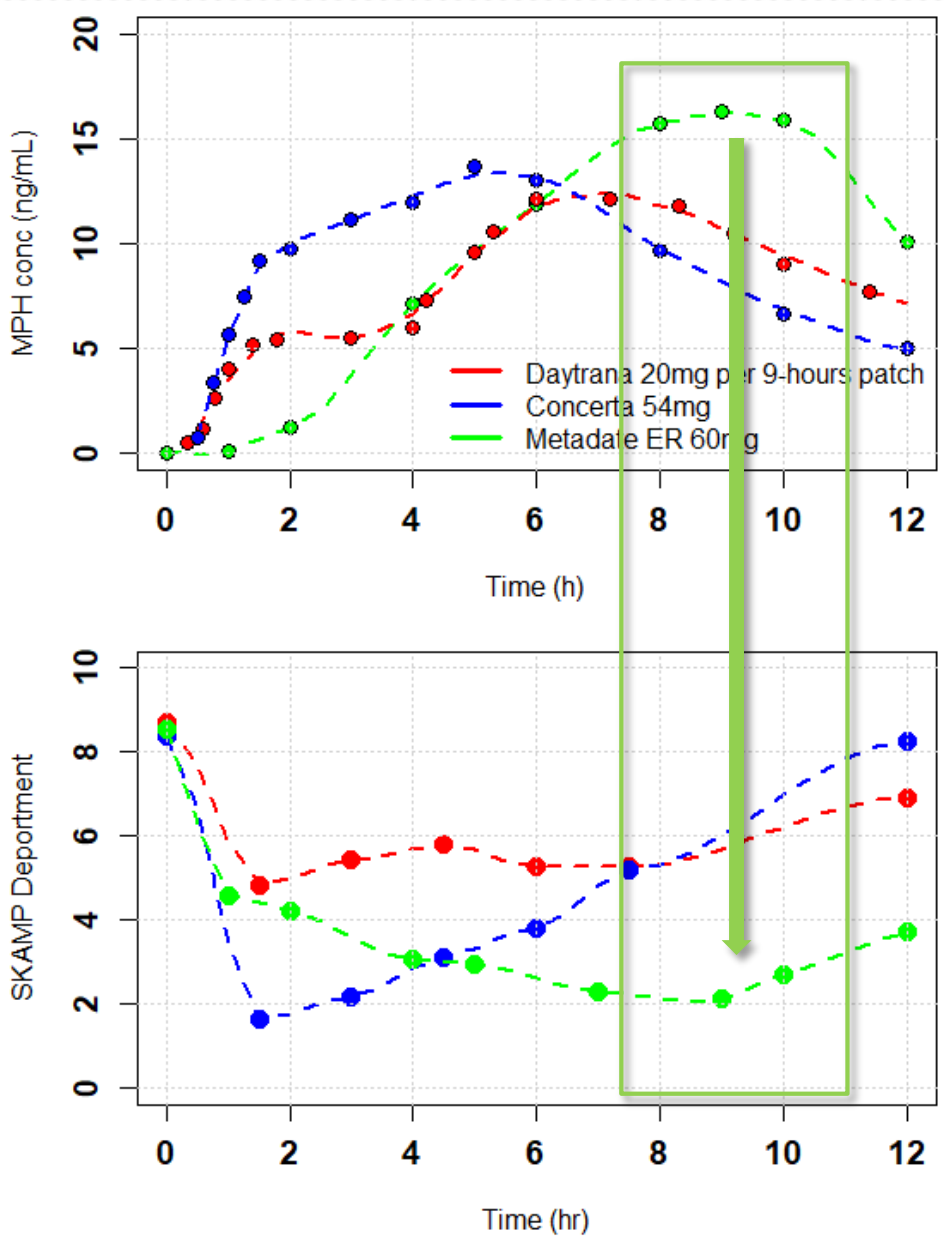


Use a meta-analytic approach for aggregating PK and PD data generated in different studies

Treatment Effect

Higher exposure

Higher response

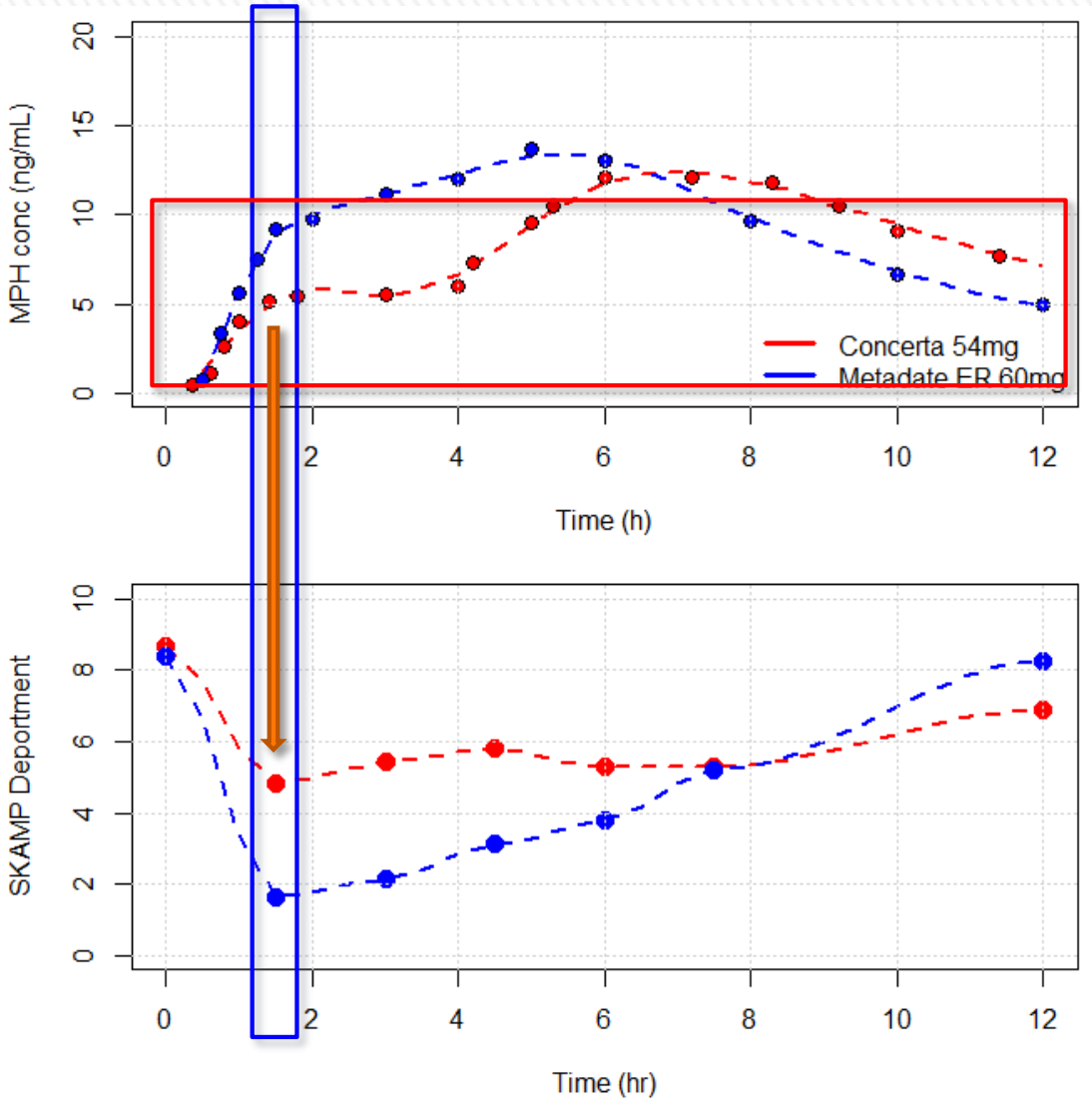


Use a meta-analytic approach for aggregating PK and PD data generated in different studies

ER Oral Formulations: Treatment Effect

For a given treatment, the larger response is **not** associated with the larger exposure

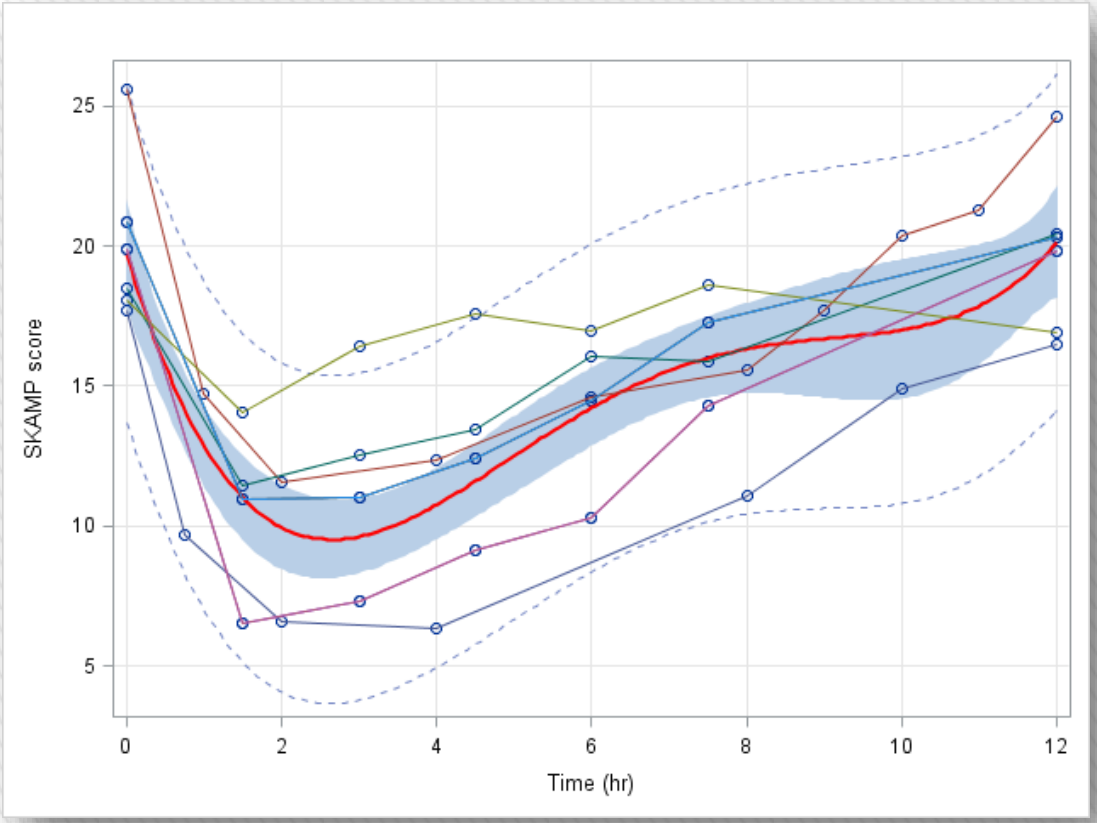
- Time-course of the longitudinal placebo response ?
- Tachyphylaxis?



Use a meta-analytic approach for aggregating PK and PD data generated in different studies

MPH response – Meta-analytic approach

Smoothing function describing the typical SKAMP trajectories from 4 clinical trials after Concerta ® (16mg, 36mg, and 54mg) , Metadate CD®(20 mg, 40 mg, and 60 mg), Focalin XR® (20 mg), and Quillivant XR® (60 mg).



- *Common longitudinal trajectory*
- *Dose related drop from baseline*

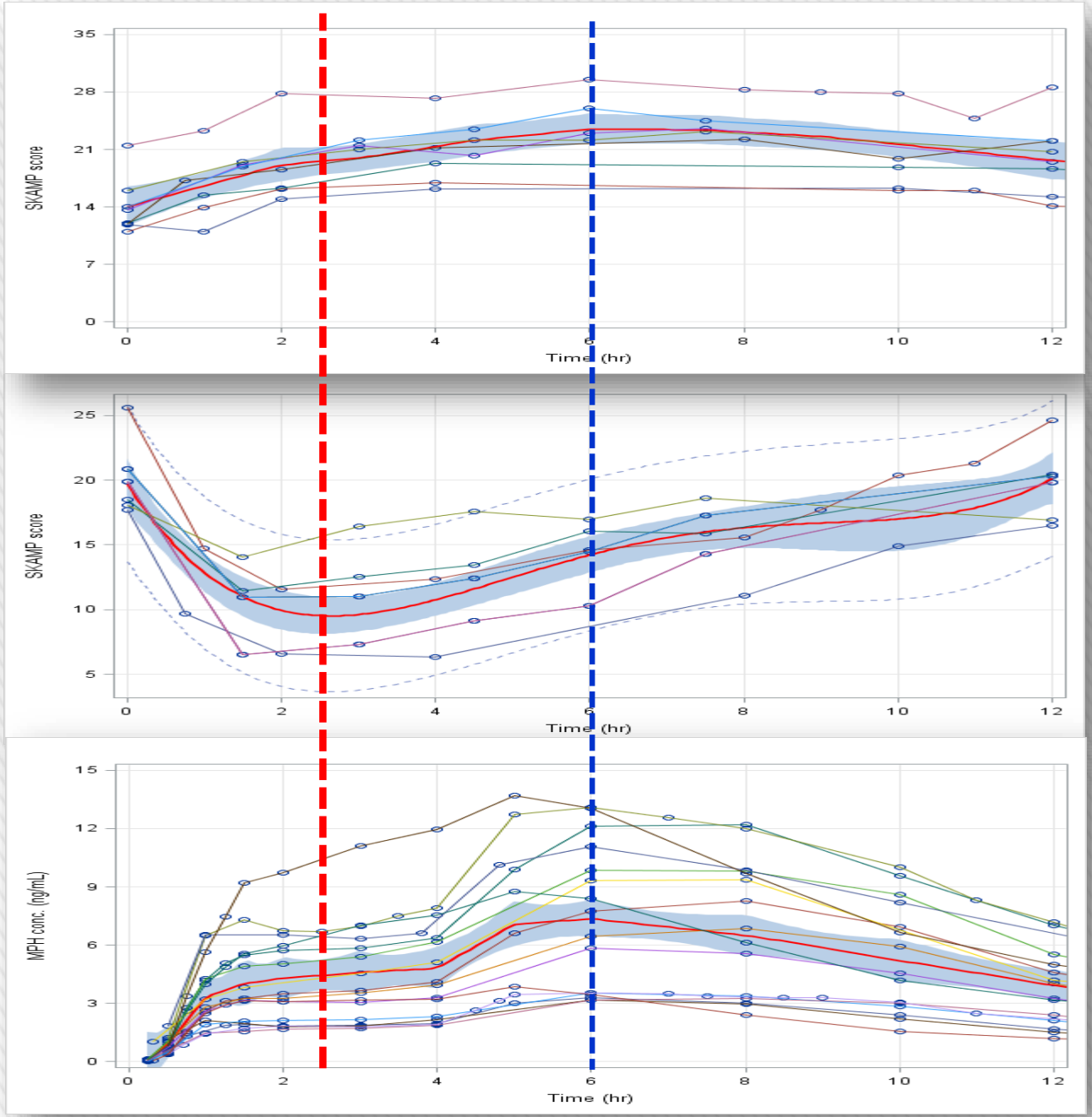
1) *Kimko H. et al. J Pharmacokinet Pharmacodyn. 2012;39(2):161-76.*
2) *Sharon B. Wigal et al., Journal Of Child And Adolescent Psychopharmacology 2013. 23(1),*
3) *Sonuga-Barke EJ. Et al BMC Psychiatry. 2004. 4:28*
4) *Raul R. Silva et al. Journal Of Child And Adolescent Psychopharmacology . 2006. 16(3)*

Placebo and MPH related response

Placebo SKAMP score

MPH SKAMP score

MPH PK Concerta® Metadate®



Modeling strategy

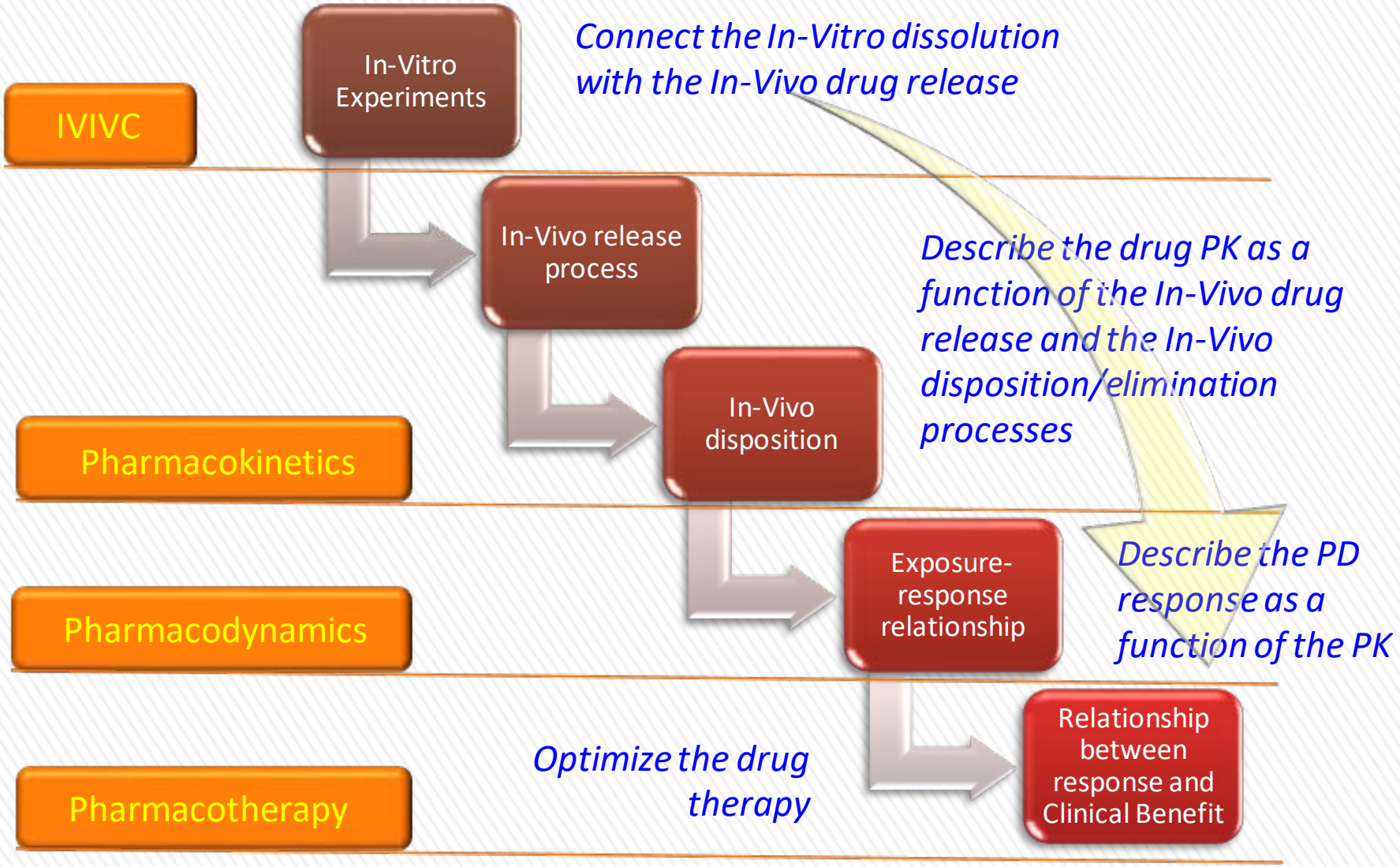
I. Characterize the complex PK of the MPH extended release products

II. Characterize the time course of the Placebo response

III. Characterize the MPH related effect on the SKAMP scores accounting for tachyphylaxis

IV. Estimate the optimal MPH dose and release rate for better controlling early morning clinical response

Integrated modelling framework

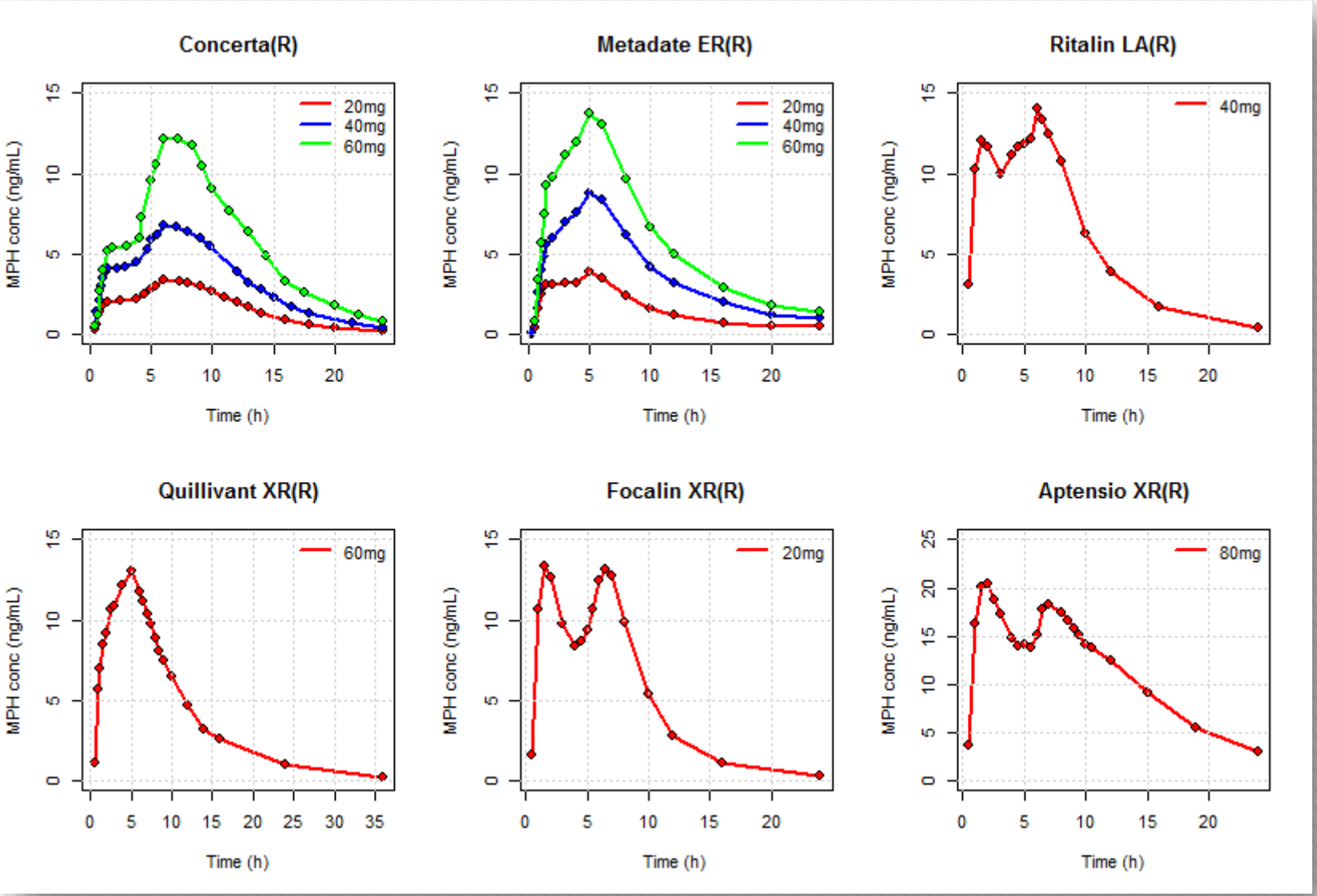


Gomeni R, Fang LL, Bressolle-Gomeni F, Spencer TJ, Faraone SV, Babiskin A. A general framework for assessing IVIVC as a tool for maximizing the benefit-risk ratio of a treatment using a convolution-based modeling approach. CPT Pharmacometrics Syst Pharmacol. 2019 Jan 18. doi: 10.1002/psp4.12378.

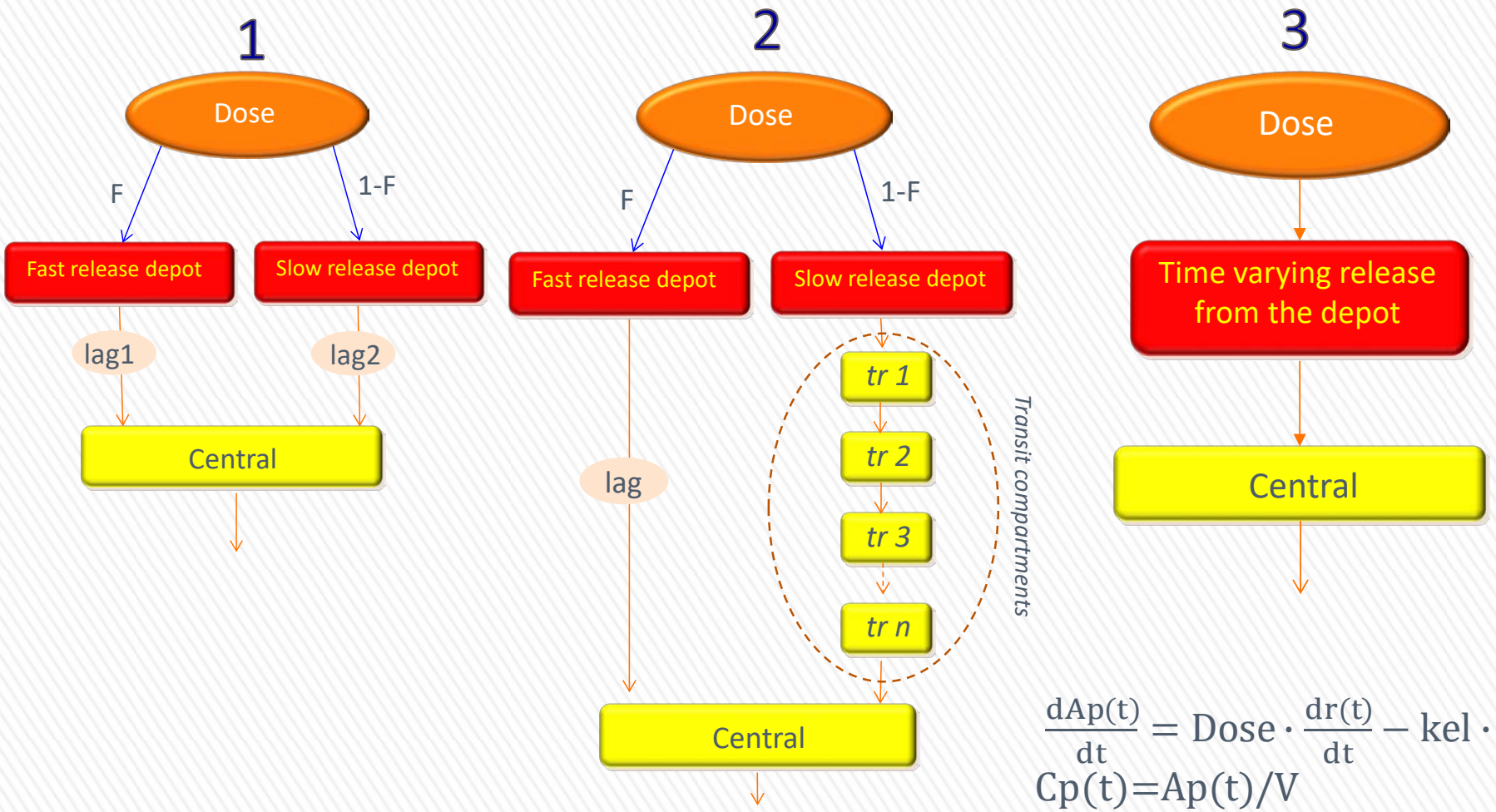
Part I

Characterize the complex PK of the MPH extended release products

PK profiles of different extender release formulations of MPH



Alternative models



$$\frac{dAp(t)}{dt} = Dose \cdot \frac{dr(t)}{dt} - kel \cdot Ap$$

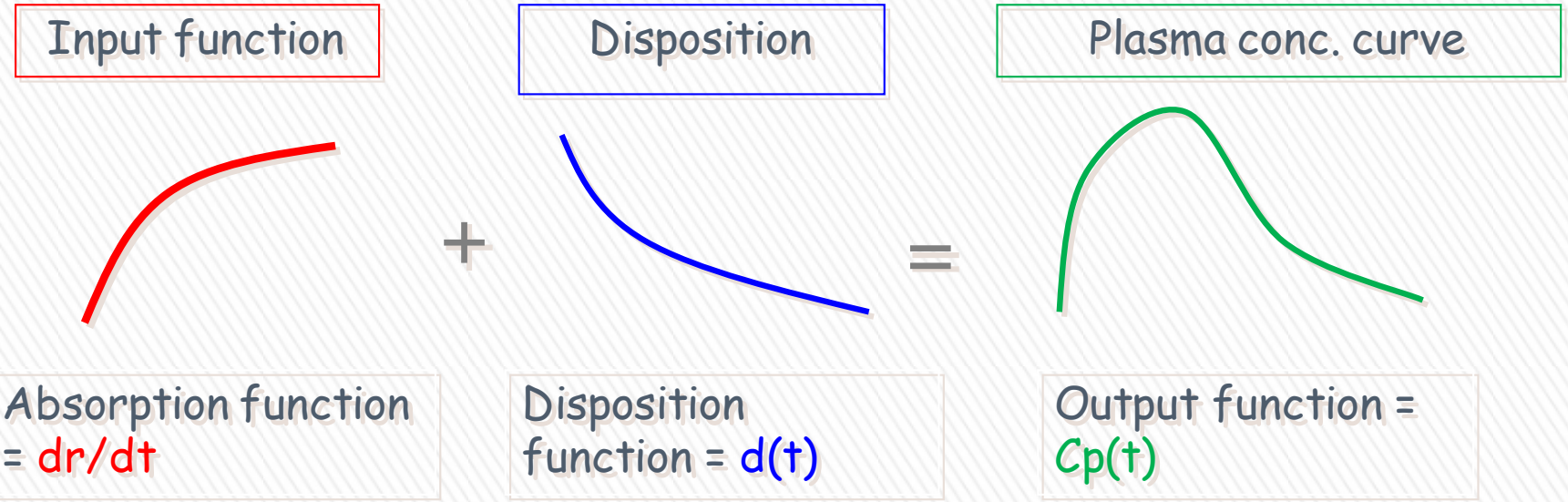
$$Cp(t) = Ap(t)/V$$

$$r(t) = 1 - \left(FF \cdot e^{-\left(\left(\frac{t}{TD}\right)^{ss}\right)} + (1 - FF) \cdot e^{-\left(\left(\frac{t}{TD1}\right)^{ss1}\right)} \right)$$

Convolution integral theory

$$Cp(t) = \int_0^t \frac{dr(\tau)}{dt} \cdot d(t-\tau) \cdot d\tau$$

The plasma drug-concentration-vs.-time curve can be viewed as the resultant of the combined processes relating drug absorption, distribution and elimination



The output function Cp(t) can be estimated as the convolution of a input function dr/dt, with a disposition function d(t) (drug disposition after IV dose)

Convolution-based PK model

The integrated PK model linking in-vivo drug release with the disposition and elimination processes can be developed using a convolution-based approach. The drug concentration (Cp), resulting from an arbitrary dose, can be described by convolution as:

$$Cp(t) = \int_0^t \frac{dr(\tau)}{dt} \cdot d(t-\tau) \cdot d\tau$$

where f(t) is the rate of in-vivo drug delivery, d(t) is the unit impulse response and * is the symbol defining the convolution.

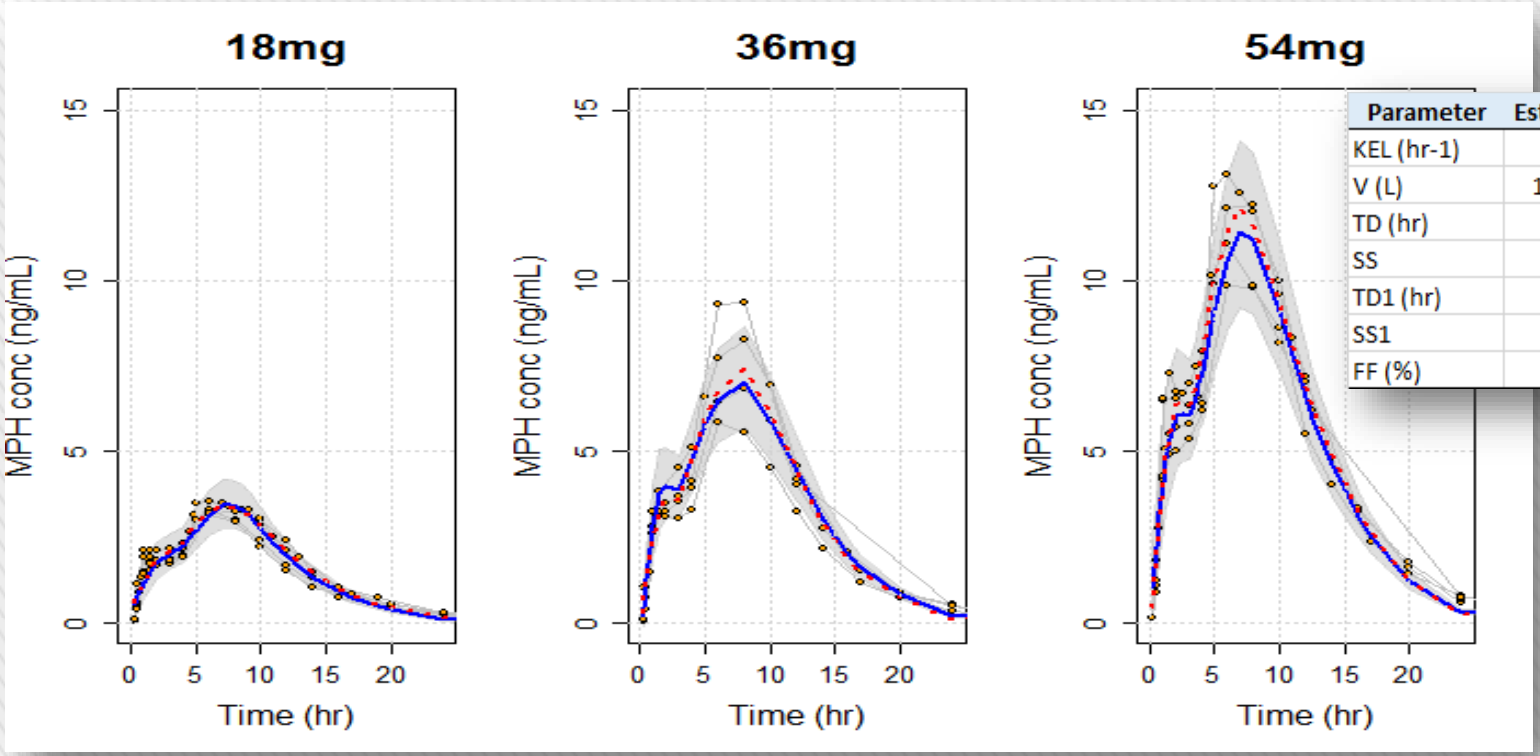
In case of a simple disposition process (say one compartment), the model equation describing Cp(t) can be written as

$$\frac{dCp}{dt} = Dose \cdot \frac{dr}{dt} - Kel \cdot Cp$$

Assuming that the time-varying fraction of the dose released can be described by the function r(t) (input function). This can be computed analytically or can be approximated using the finite difference approach (see an example of implementation in NONMEM)

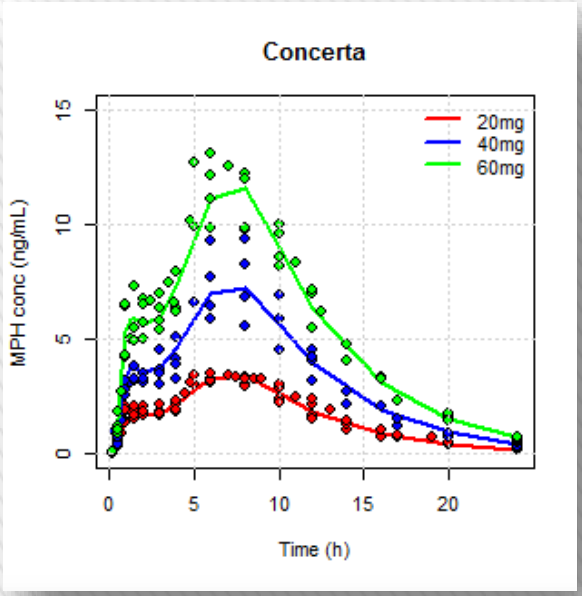
Convolution-based model used to fit Concerta® data

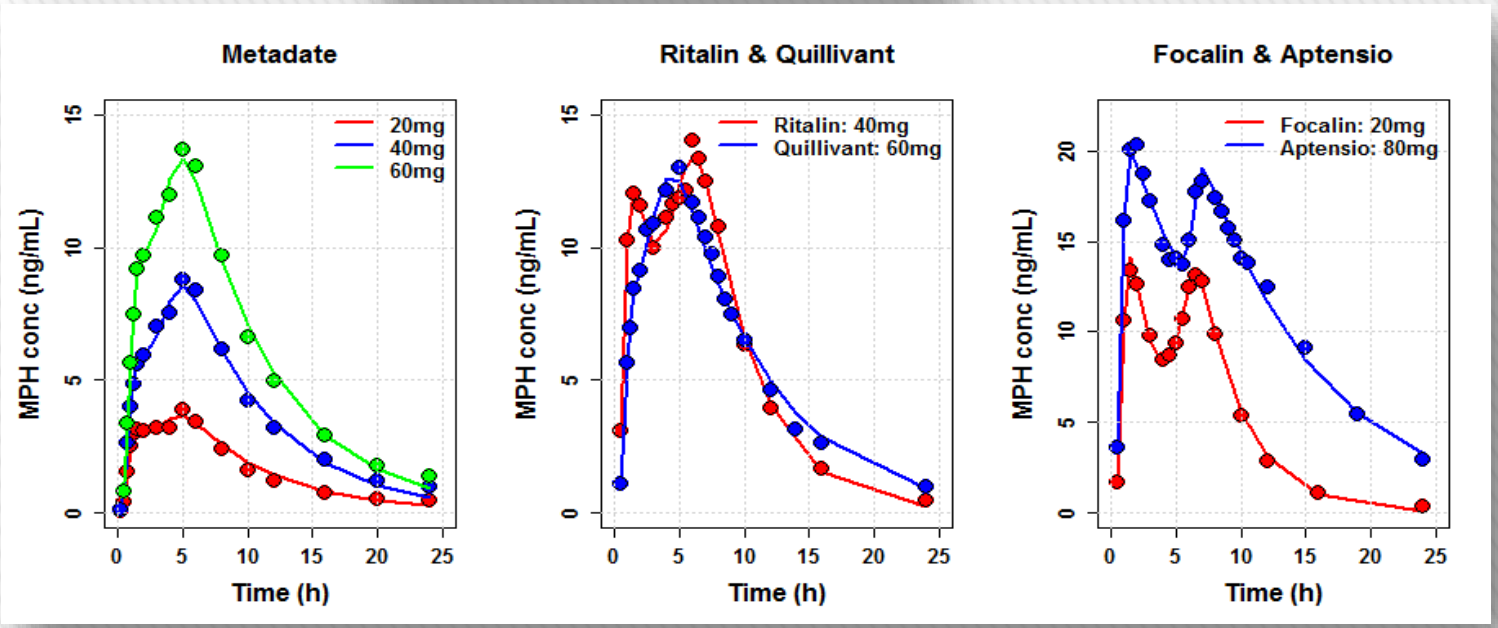
- Data extracted from 9 publications describing the MPH PK following administration of Concerta ® (16mg, 36mg, and 54mg) were used for model building
- The convolution-based approach performed better then the other models



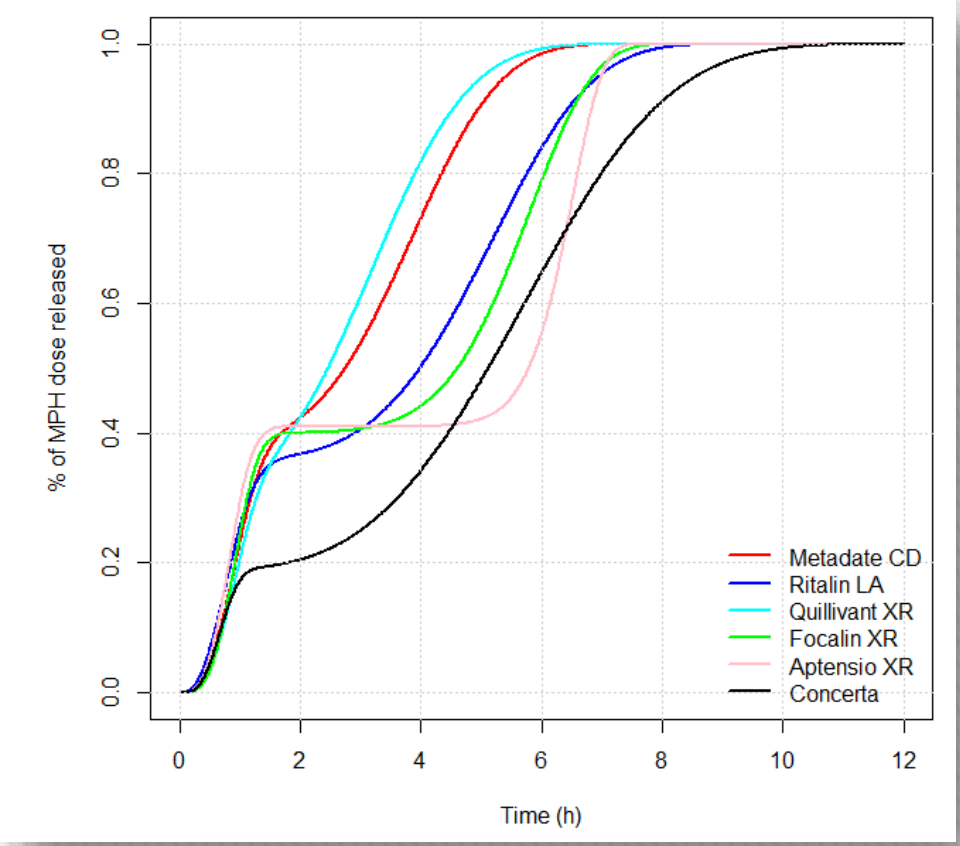
Parameter	Estimate	SE	RSE
KEL (hr-1)	0.18	0.00	1.70%
V (L)	1600.00	60.00	3.80%
TD (hr)	0.76	0.04	5.60%
SS	3.18	0.09	2.80%
TD1 (hr)	6.33	0.10	1.50%
SS1	3.40	0.09	2.70%
FF (%)	0.19	0.01	5.00%

Fit 6 MPH formulations PK data with the same model





Comparing in-vivo release of 6 MPH products



f = fraction of the dose released in the 1st process

td = time to absorb 63.2% of the dose released in the 1st process

td1= time to absorb 63.2% of the dose released in the 2nd process

ss= sigmoidicy factor for the 1st process

ss1= sigmoidicity factor for the 2nd process

	td (hours)	ss	ss1	td1 (hours)	ff (%)	td_99% (hours)	td1_99% (hours)
Metadate CD®	1.04	2.87	3.68	4.21	39%	1.64	6.19
Ritalin LA®	0.92	2.6	4.18	5.55	36%	1.51	7.8
Quillivant XR®	1.03	2.99	2.98	3.64	32%	1.57	5.91
Focalin XR®	1.02	3.41	6.56	5.96	40%	1.5	7.39
Aptensio XR®	0.93	3.15	6.56	14.3	59%	1.46	7.2
Concerta®	0.76	3.18	3.4	6.33	19%	1.07	9.79

Linking In-vitro and in-vivo release: the convolution-based model

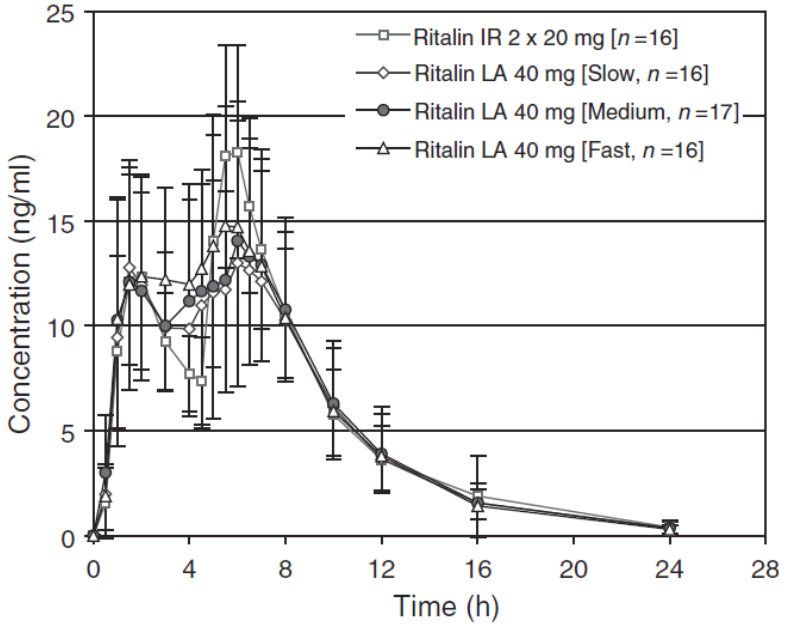


Figure 1. Plasma concentration (mean ± SD)-time profile of MPH after a single dose of Ritalin LA slow-, medium- or fast-release formulation and Ritalin tablets (immediate release formulation) given 4 h apart

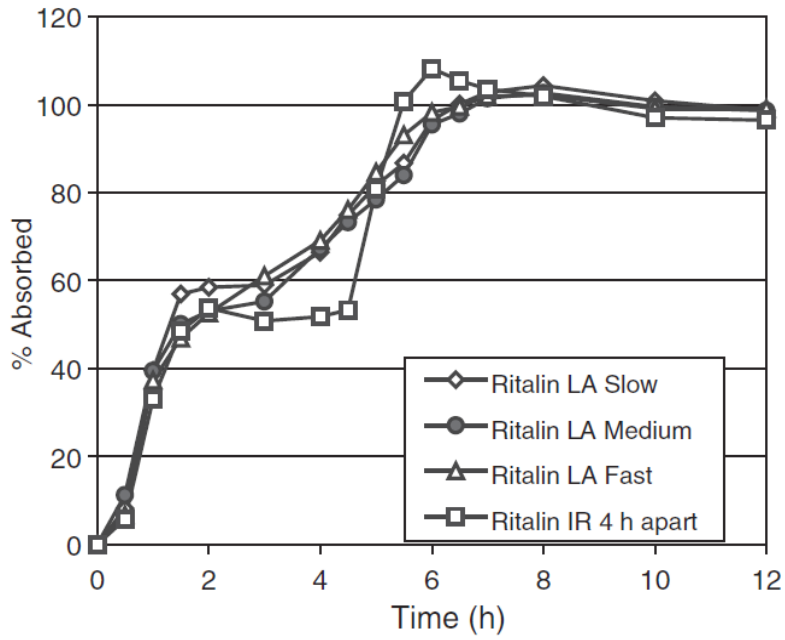
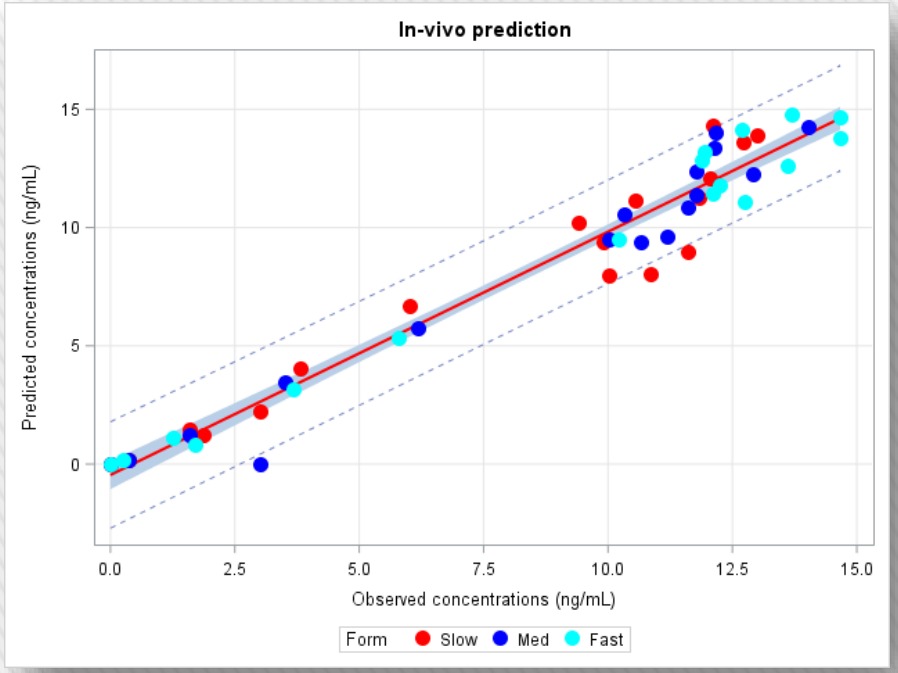


Figure 3. Cumulative fraction of MPH absorbed from Ritalin LA slow-, medium- and fast-release formulations and from Ritalin-IR tablet given 4 h apart

Wang Y, Lee L, Somma R, Thompson G, Bakhtiar R, Lee J, Rekhi GS, Lau H, Sedek G, Hossain M. In vitro dissolution and in vivo oral absorption of methylphenidate from a bimodal release formulation in healthy volunteers. Biopharm Drug Dispos. 2004 Mar;25(2):91-8.

Evaluating the IVIVC



Parameter Estimates							
Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	95% Confidence Limits	
Intercept	1	-0.45953	0.29739	-1.55	0.1286	-1.05685	0.13779
Observed PK	1	1.02828	0.03058	33.63	<.0001	0.96686	1.08969

$$PE = \frac{1}{n}\sum_{1}^{n}\frac{|\text{Obs. value} - \text{Pred. value}|}{\text{Obs. value}} \cdot 100$$

0 - 24 hr						
Formulation	cmax_o	auc_o	cmax_p	auc_p	pe_cmax	pe_auc
Slow	13.01	127.46	14.35	127.36	10.28	0.08
Medium	14.02	130.86	14.25	122.92	1.64	6.07
Fast	14.67	133.44	14.79	126.75	0.87	5.01
				Average	4.26	3.72

Predictability criteria:

- PE <15% for each formulation,
- PE <10% for mean values

0 - 3 hr			
Formulation	auc_o	auc_p	pe_auc
Slow	14.70	15.09	2.62
Medium	16.99	16.30	4.05
Fast	15.18	14.79	2.62
		Average	3.10

3 - 7 hr			
Formulation	auc_o	auc_p	pe_auc
Slow	44.70	41.71	6.68
Medium	46.70	46.15	1.18
Fast	45.96	47.16	2.62
		Average	3.49

7 - 12 hr			
Formulation	auc_o	auc_p	pe_auc
Slow	26.25	28.44	8.35
Medium	25.96	23.80	8.36
Fast	36.63	32.59	11.03
		Average	9.24

CPT Pharmacometrics Syst Pharmacol. 2019 Jan 18. doi: 10.1002/psp4.12378.

Part II

Characterize the time course of the Placebo response

Disease Progression Model

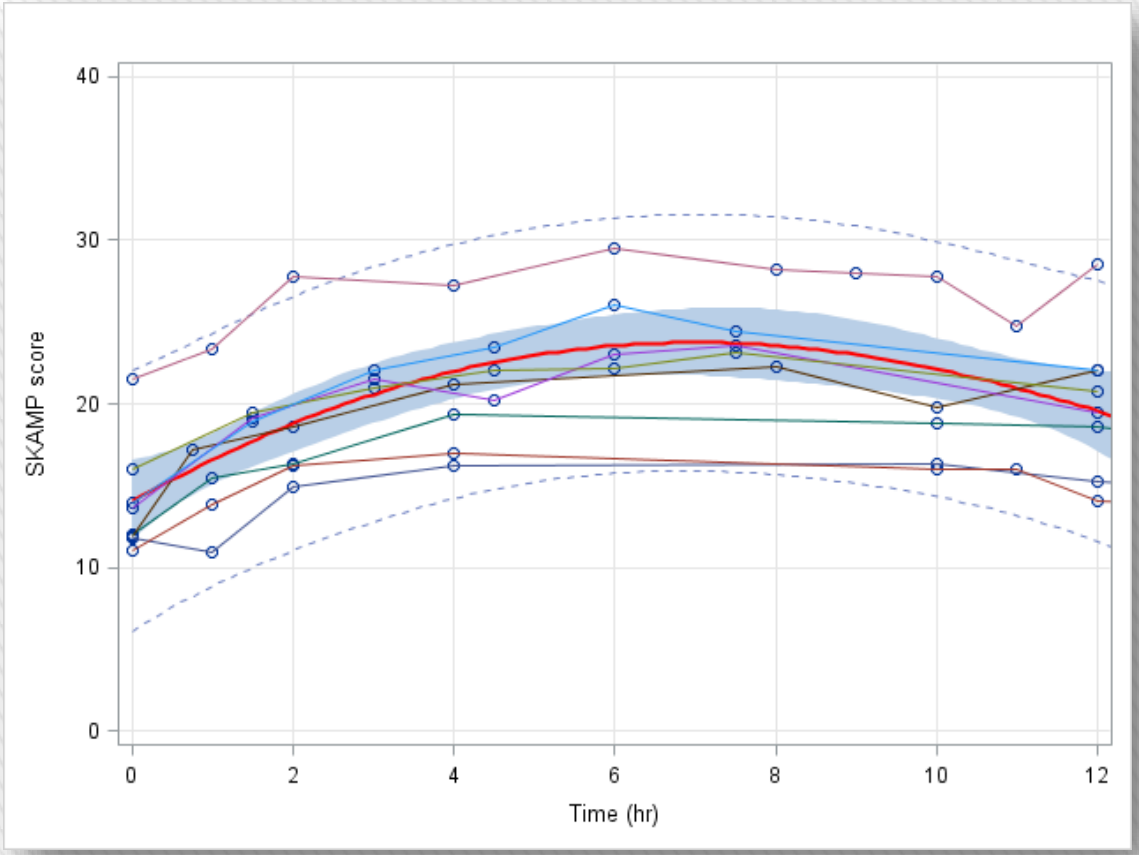
Disease Progression Model: A quantitative model that accounts for the time course of disease status, S(t):

- *Baseline Disease State*
- *Natural History*
- *Placebo Response*
- *Active Treatment Response*

S(t) = Natural History + Placebo + Active

Placebo data – Meta-analytical approach

Smoothing function describing the typical mean SKAMP placebo trajectories from 4 clinical trials



1) *Kimko H. et al. J Pharmacokinet Pharmacodyn. 2012;39(2):161-76.*
2) *Sharon B. Wigal et al., Journal Of Child And Adolescent Psychopharmacology 2013. 23(1),*
3) *Sonuga-Barke EJ. Et al BMC Psychiatry. 2004. 4:28*
4) *Raul R. Silva et al. Journal Of Child And Adolescent Psychopharmacology . 2006. 16(3)*

Semi-mechanistic Placebo response model

The rate of change of the response (R = SKAMP score) was described by:

$$\frac{dR}{dt} = K_{in} \cdot (1 + f(t)) - K_{out} \cdot R$$

where k_{in} represents the zero-order rate constant for onset of response, R, and k_{out} is the first-order rate constant for the loss of response variable.

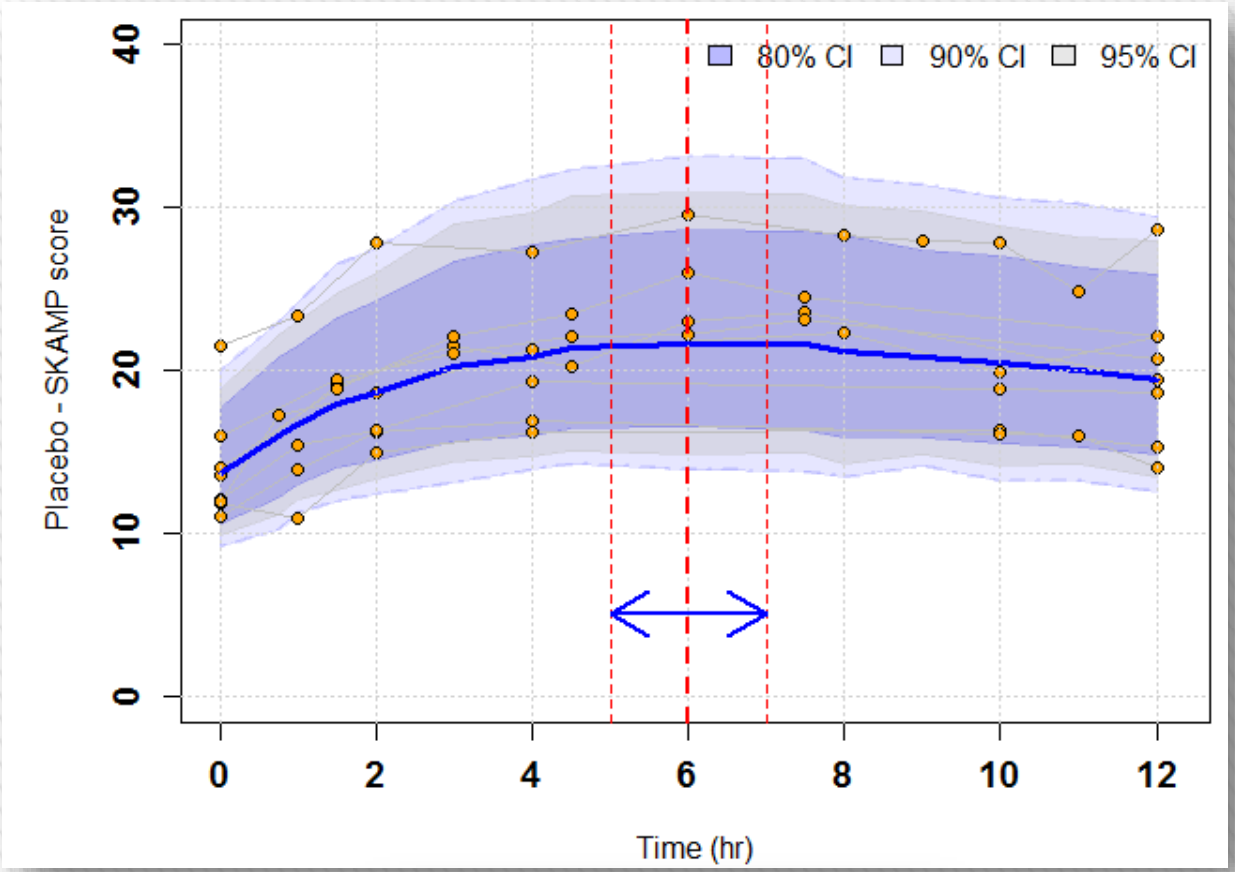
As the system is assumed to be stationary, the response (R) begins at a predetermined baseline value (Bas), changes with time, and eventually returns back to $R0$.

$$f(t) = AA \cdot e^{-time \cdot A1}$$ *Time varying placebo effect*

$$\mathrm{R}(t = 0) = Bas = \frac{K_{in}}{K_{out}}$$ *Baseline SKAMP score*

$$K_{in} = K_{out} \cdot Bas$$

Placebo response – Modelling results



Parameter	Estimate	SE	RSE
BAS	12.70	1.040	8.20%
KOUT	0.15	0.008	5.00%
A1	0.16	0.008	5.10%
AA	1.85	0.162	8.80%

The dark blue area represent the 80% prediction intervals and the light blue area represent the 90% and the 95% prediction intervals

Part III

Characterize the MPH related effect on the SKAMP scores

Tachyphylaxis

Methylphenidate exhibit acute tolerance :concentrations measured soon after an initial dose cause a greater pharmacodynamic effect then concentrations occurring at a later time

- The EC_{50} (the MPH concentration giving 50% of the maximal effect) increase with time
- This assumption translate the observation that the effect associated with a constant MPH exposure decline with time: as time passes, higher EC50 -> more drug is needed to achieve the same effect*

$$EC_{50}(t) = EC_{50b}\left(1+\frac{time^{ga}}{t50^{ga}+time^{ga}}\right)$$

Where:

EC_{50} (t)= effective time varying EC_{50} value

EC_{50b}= EC_{50} at time 0

t50 = time at which 50% of the maximal change in EC_{50}(t) is reached

ga = rate of change in the EC_{50}(t)

Kimko et al. Journal of pharmacokinetics and pharmacodynamics 2012;39:161-76

MPH clinical response model

$$\boldsymbol{SKAMP(effect) = R(t) + Delta - \frac{Emax \cdot C_p}{EC_{50}(t) + C_p}}$$

Where:

R(t) is the placebo response defined by the model

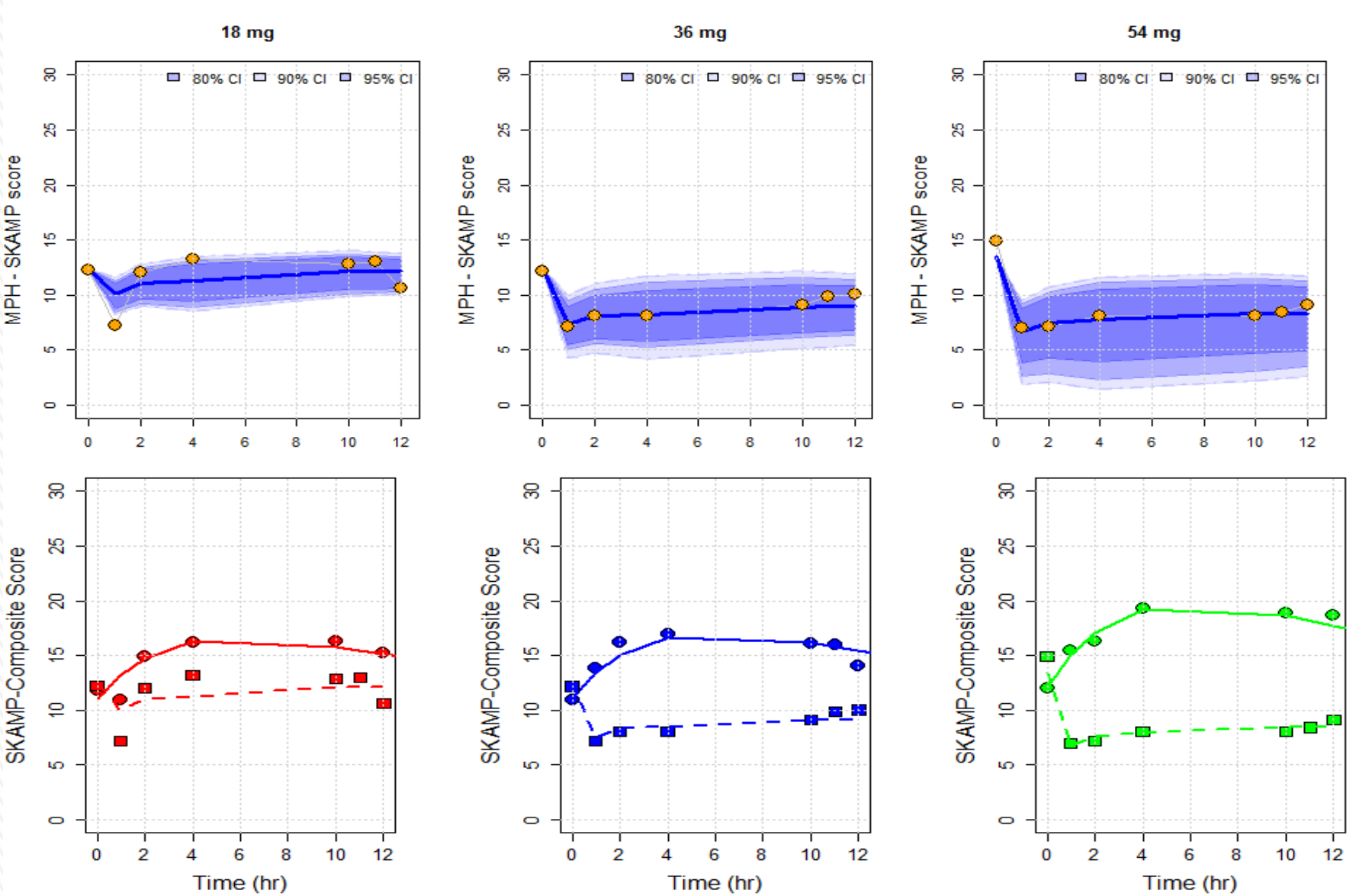
$$\frac{dR}{dt} = k_{in} \cdot \left(1 + f(t)\right) - k_{out}R$$

EC50(t) is the time varying EC50 defined by the model

$$EC_{50}(t) = EC_{50b}\left(1 + \frac{time^{ga}}{t50^{ga} + time^{ga}}\right)$$

Delta is the score difference at baseline depending on the treatment between assessment days
Emax is the maximal MPH related effect
Cp is the MPH drug concentration

The PK/PD model



R Gomeni, F. Bressolle-Gomeni, TJ Spencer, SV Faraone, L Fang, A Babiskin. Model-Based Approach for Optimizing Study Design and Clinical Drug Performances of Extended-Release Formulations of Methylphenidate for the Treatment of ADHD. Clin Pharmacol Ther. 2017 Dec;102(6):951-960.

Part IV

Estimate the optimal MPH dose and iv-vivo release rate for optimizing the clinical benefit of a treatment

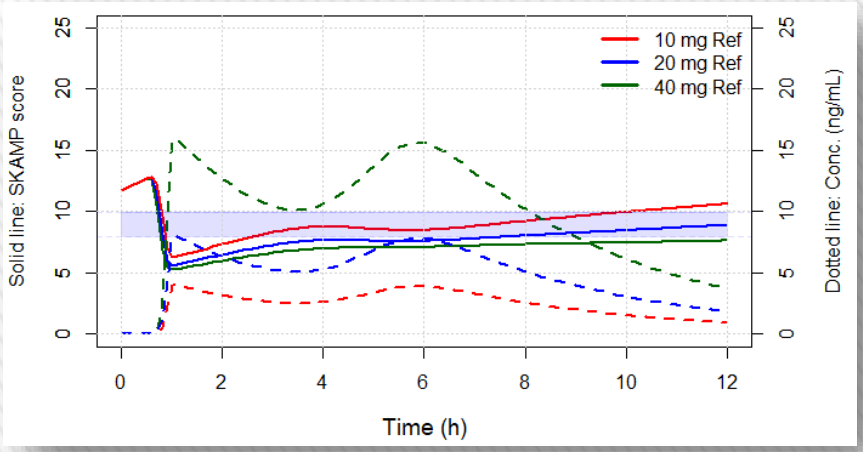
Clinical benefit

$$SKAMP(effect) = P(t) + Delta - \frac{Emax \cdot C_p}{EC_{50} + C_p}$$

$$r_{vitro}(t) = Dose \cdot \left[1 - \left(ff \cdot e^{-\left(\left(\frac{time}{td}\right)^{ss}\right)} + (1 - ff) \cdot e^{-\left(\left(\frac{time}{td1}\right)^{ss1}\right)}\right)\right]$$

$$f(t) = \frac{dr_{vivo}}{dt}$$

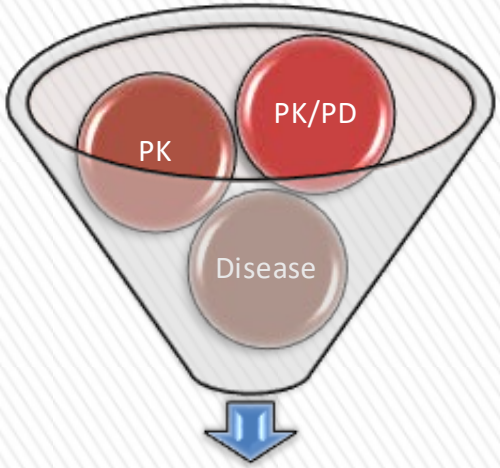
$$\frac{dA}{dt} = F_i * Dose * f(t) - k_{el} \cdot A \Rightarrow Cp = \frac{A}{V}$$



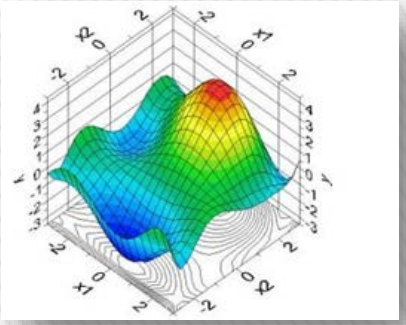
CB=f(SKAMP)

SKAMP=f(Cp)

Cp(ff, ss, ss1, td, td1, Dose)



Response variable = Clinical benefit



CB: maintenance of SKAMP scores from 8 to 10 during 12 hours was considered as the target clinical response

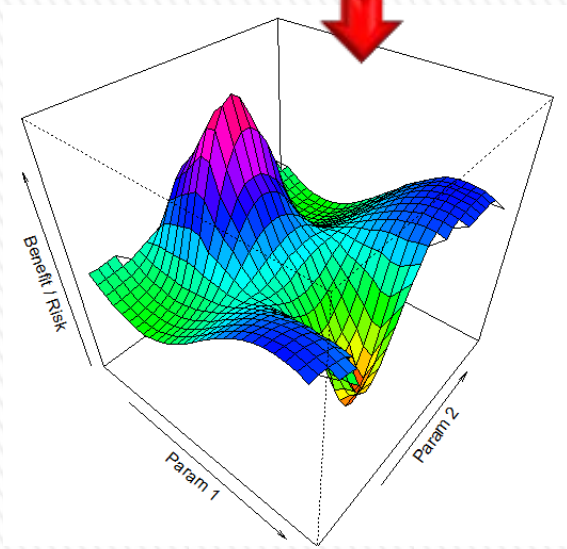
Response Surface Analysis and Nonlinear Optimization Algorithm for Maximization of Clinical Benefit

Benefit/risk parameters
- Dose & Dosage regimen
- In-vitro dissolution rate

Convolution-based PK Model

PK/PD Model

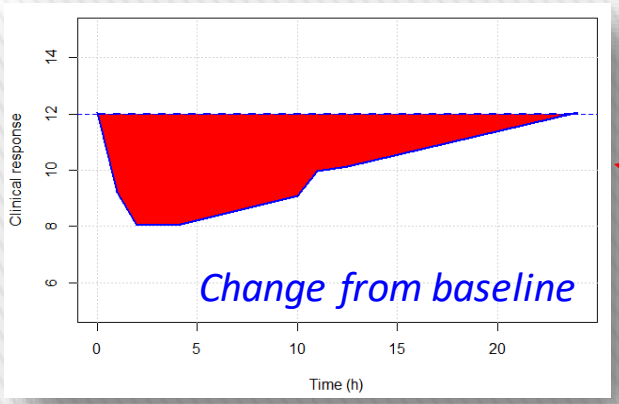
Benefit/risk

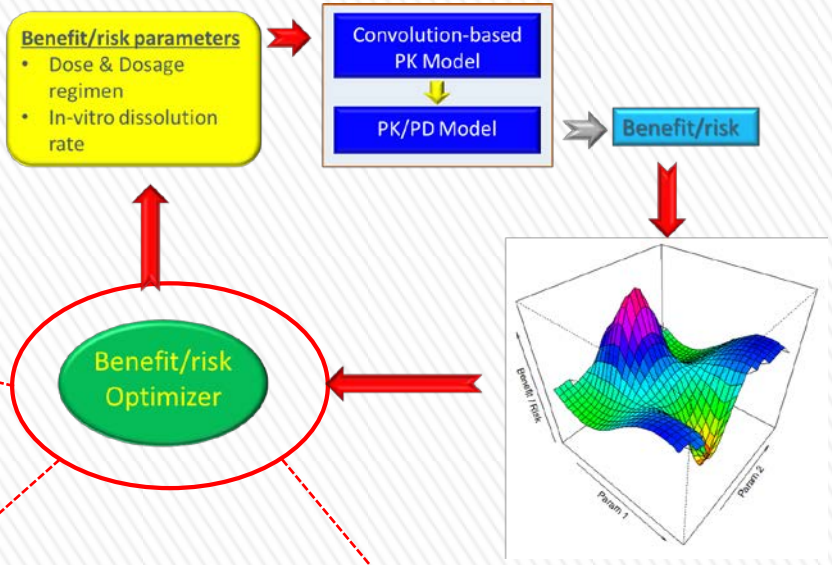


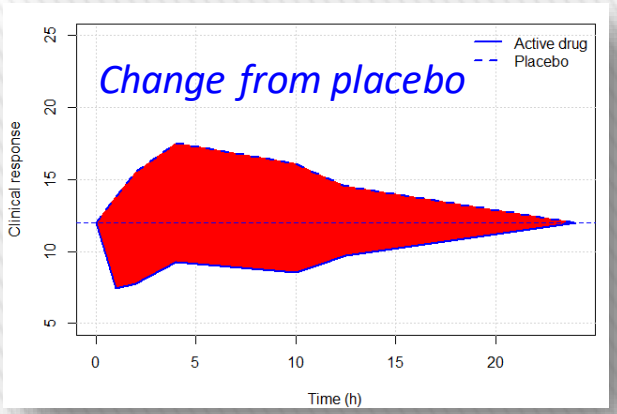
Benefit/risk Optimizer

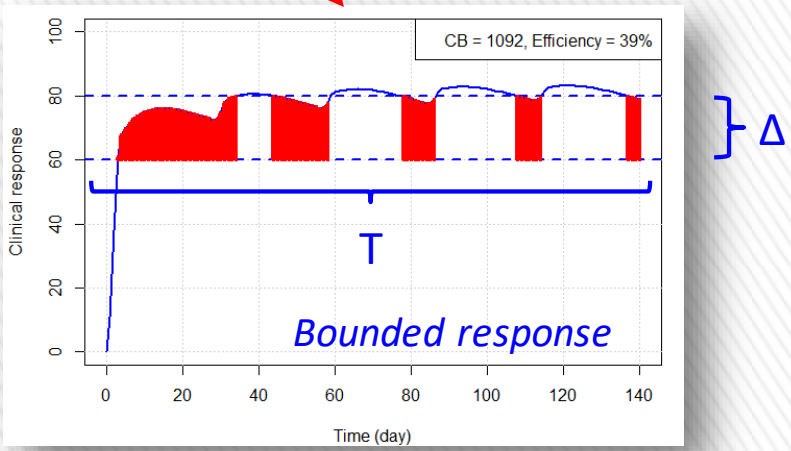
R Gomeni, FMM Bressolle-Gomeni, TJ Spencer, SV Faraone, L Fang, A Babiskin. Model-Based Approach for Optimizing Study Design and Clinical Drug Performances of Extended-Release Formulations of Methylphenidate for the Treatment of ADHD. Clin Pharmacol Ther. 2017 Mar 29. doi: 10.1002/cpt.684

Clinical Benefit





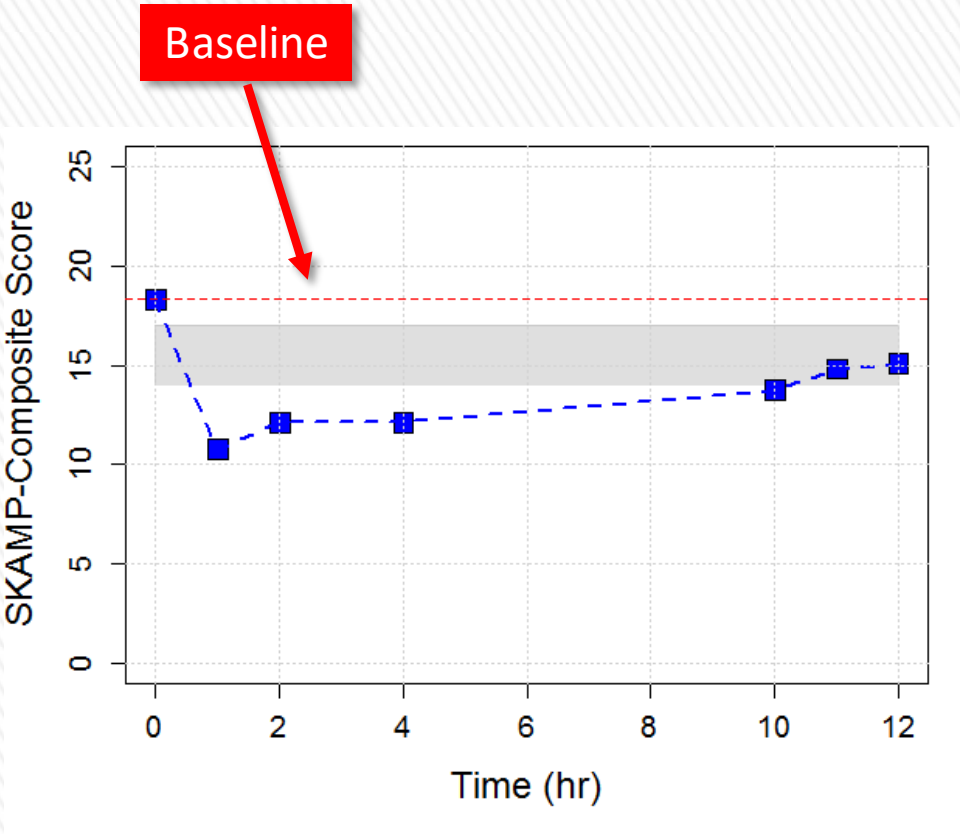




Clinical benefit in the treatment of ADHD

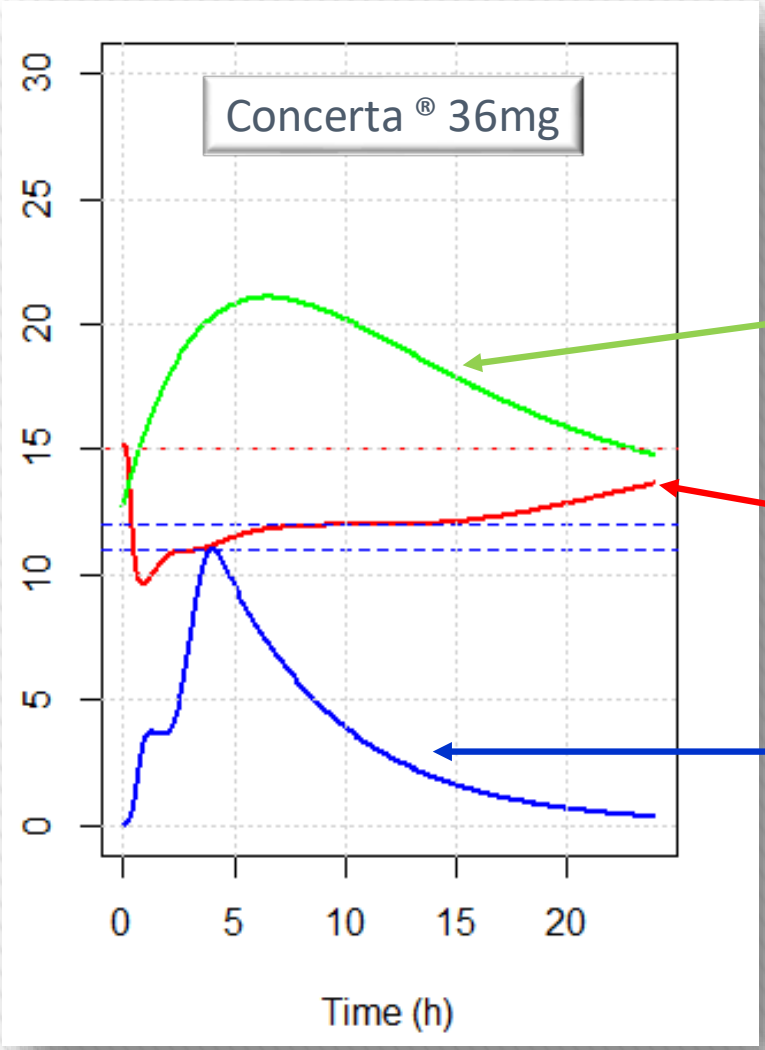
Question : what is the ideal MPH ER dose and in-vivo release for

- an initial improvement in the SKAMP score (say for example a drop of 15% of the baseline value after one hour from drug intake)
- a maintenance of this improvement during 8 consecutive hours?



Target region for the clinical response

Reference treatment

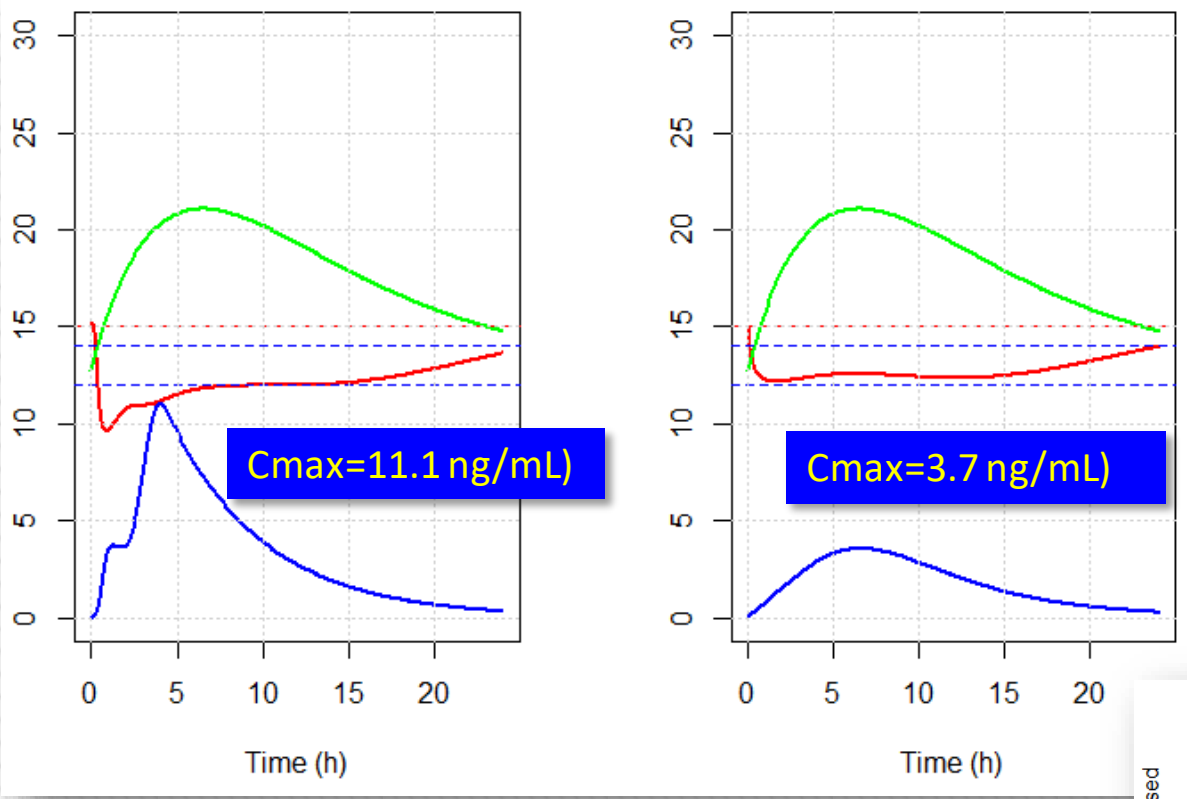


SKAMP score:
Placebo response

SKAMP score:
Concerta® response

MPH concentrations
time course

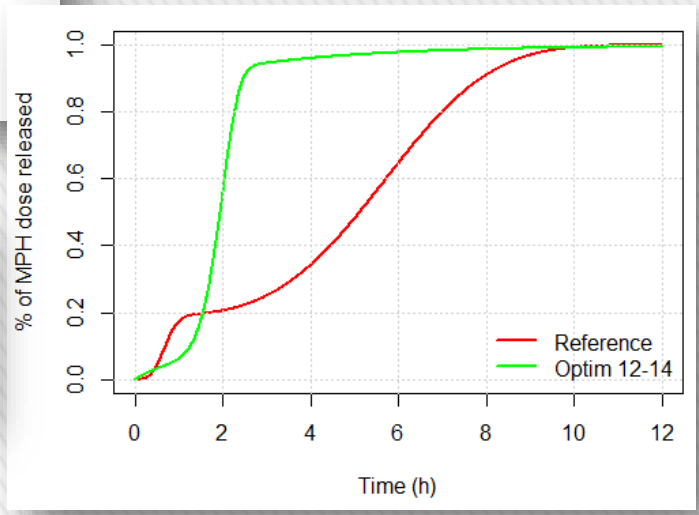
Model prediction



Optimize MPH dose and MPH in-vivo release rate

- *SKAMP score between 12 and 14*
- *Variable dose*

	SKAMP		In-Vivo release					Dose
	Min	Max	td (hr)	ss	td1 (nr)	ss1	ff (%)	(mg)
Reference			0.76	3.18	3.40	6.33	0.19	36
Optimal	12	14	2.72	0.87	6.36	2.06	0.16	20



Exposure-response of blood pressure and heart rate for methylphenidate in healthy adults

J Pharmacokinet Pharmacodyn (2017) 44:245–262
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ORIGINAL PAPER

Exposure–response analyses of blood pressure and heart rate changes for methylphenidate in healthy adults

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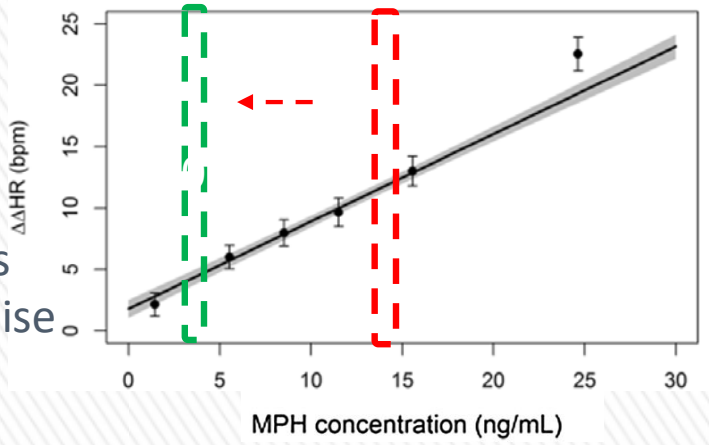
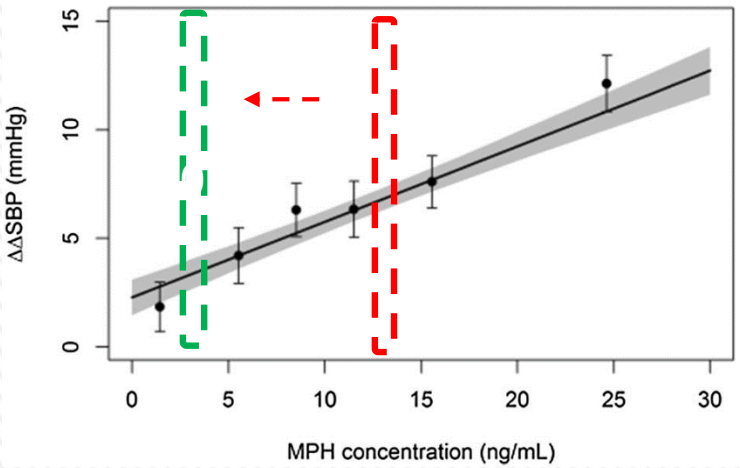
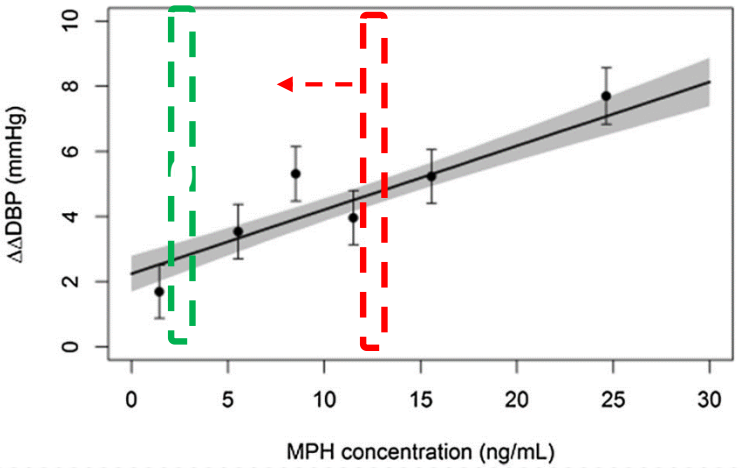
Conclusion: The developed models adequately characterized the circadian rhythm and the MPH induced effects on BP and HR. The changes in BP and HR were highly correlated with MPH blood levels with no apparent delay.

Exposure–response analyses of blood pressure and heart rate changes for MPH in healthy adults

The exposure-response of blood pressure (BP) and heart rate (HR) for MPH in healthy adults indicated that the BP and HR changes were directly related and highly dependent on the MPH plasma concentration. These safety issues associated with MPH treatment may compromise the treatment course of ADHD in children and also raise parents' concerns over them.







Li L, Wang Y, Uppoor RS, Mehta MU, Farchione T, Mathis MV, Zhu H. Exposure-response analyses of blood pressure and heart rate changes for methylphenidate in healthy adults. J Pharmacokinet Pharmacodyn. 2017 Jun;44(3):245-262. doi: 10.1007/s10928-017-9513-5.

Conclusion

- A model-informed approach can be used for identifying the best performing *in-vivo* delivery rate appropriate for maximizing the benefit-risk ratio and for facilitating the development of a formulation with the required characteristics using *in-vitro*/*in-vivo* correlation.
- The surface-response analysis can be prospectively applied for optimizing the drug development process by identifying the drug properties associated with an optimized benefit-risk.
- The proposed model-informed approach provides the pharmaceutical companies with a methodological framework for developing drugs with drug delivery and a dose selection suitable to produce a clinical benefit prospectively defined by the clinicians and not just a clinical response better than the placebo response.

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Thank you

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