

A general in-silico framework for maximizing the benefit- risk ratio of a treatment

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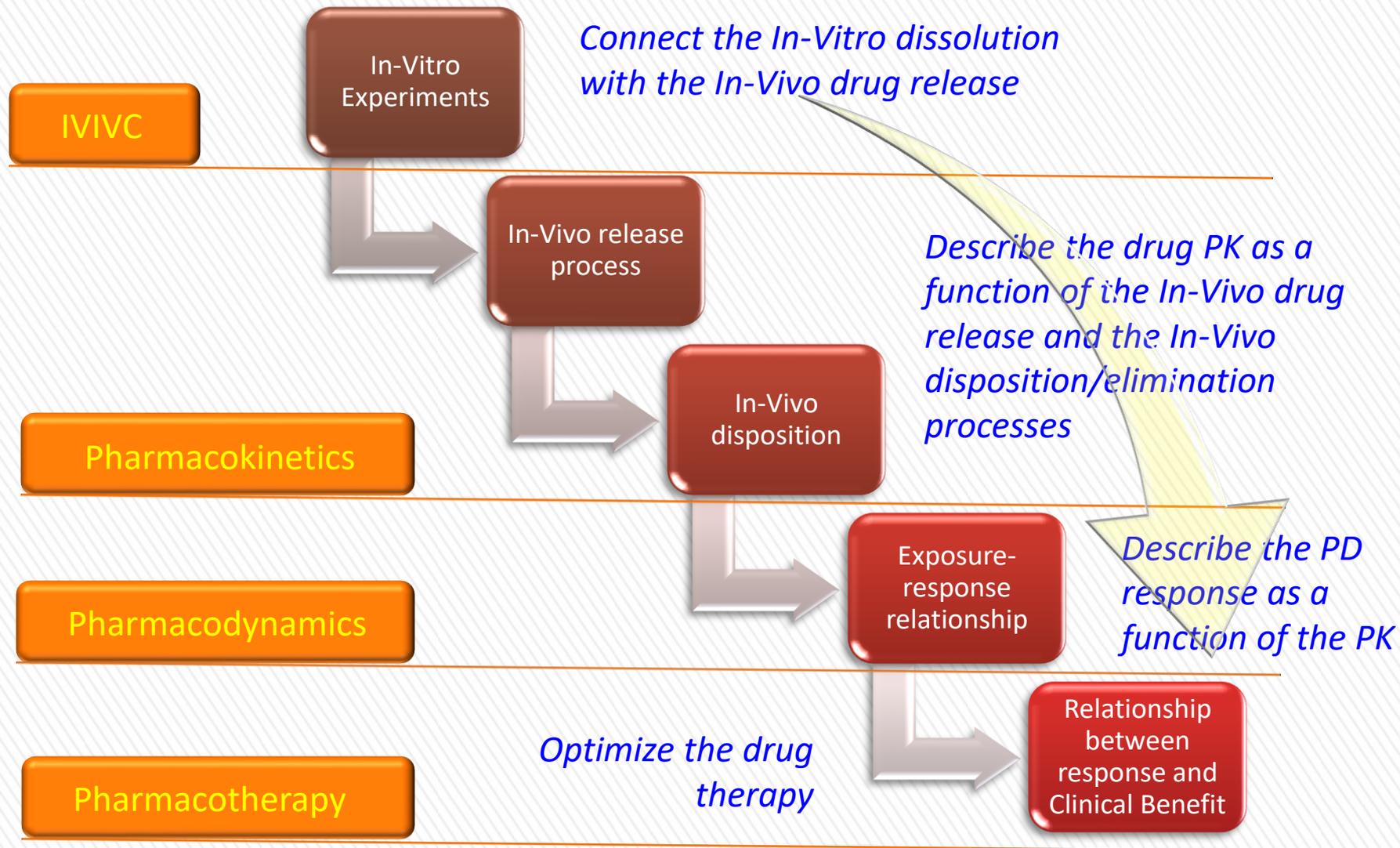
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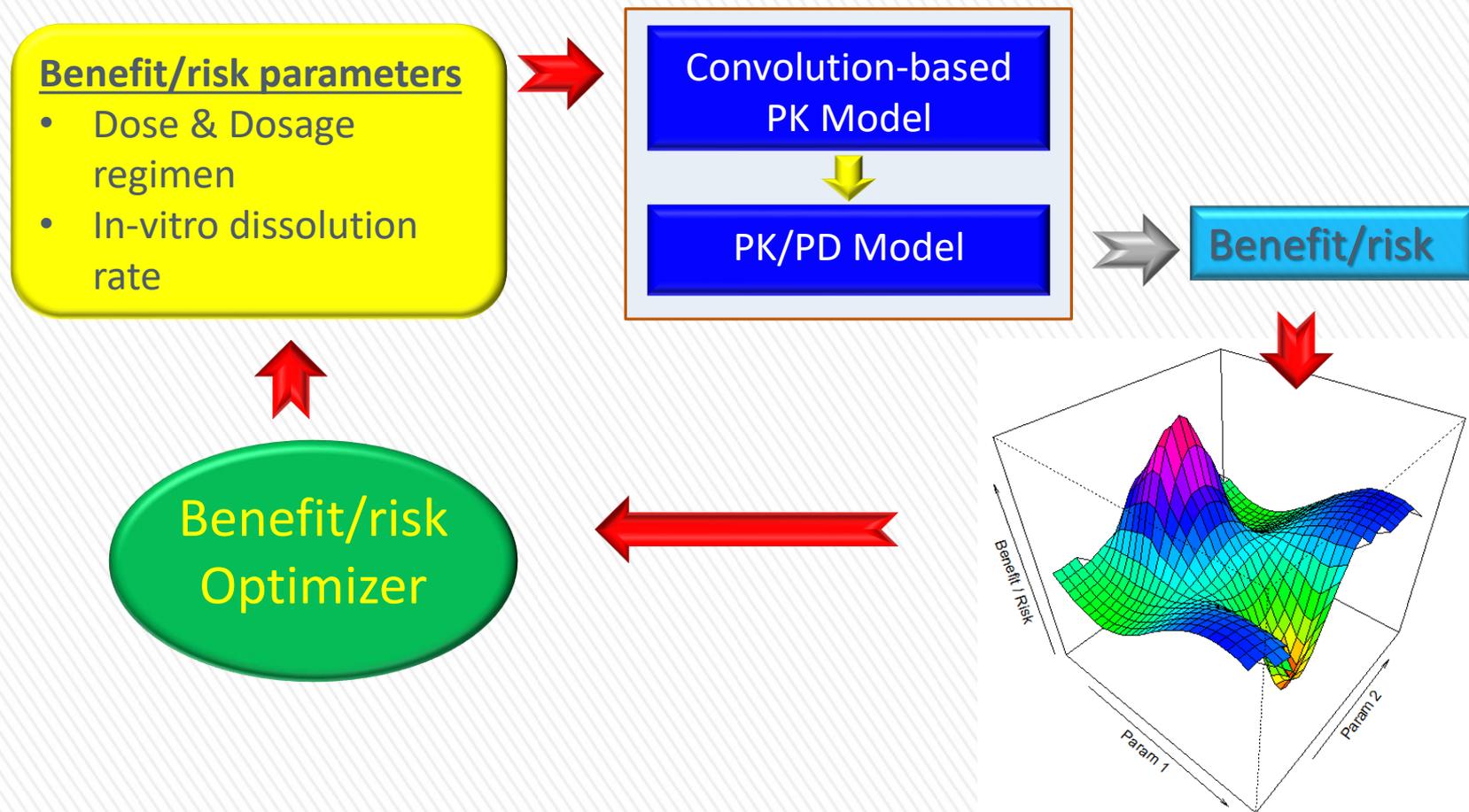
Benefit-Risk

- The clinical benefit (CB) of a treatment is usually defined in relation to the size of the treatment effect, such as the baseline corrected change from placebo at study end.
- The level of efficacy cannot be considered as the unique criterion for determining the CB of a treatment as the safety and tolerability information need to be accounted for.
- A better definition of the CB of a pharmacological treatment should be based on the concept of benefit-risk ratio.
- Accordingly, CB can be defined as a treatment effect with a size sufficiently large to constitute a real clinical improvement with a minimal risk of adverse events.
- The convolution-based modeling approach has been proposed as a tool for optimizing the CB of a pharmacological treatment.
- The CB optimization can be achieved by identifying the best performing dose and dosage regimen jointly with the best performing *in vivo* release properties of the drug.

Modelling components

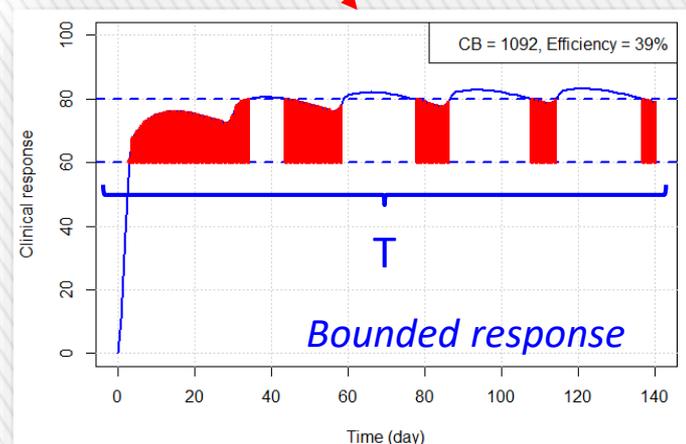
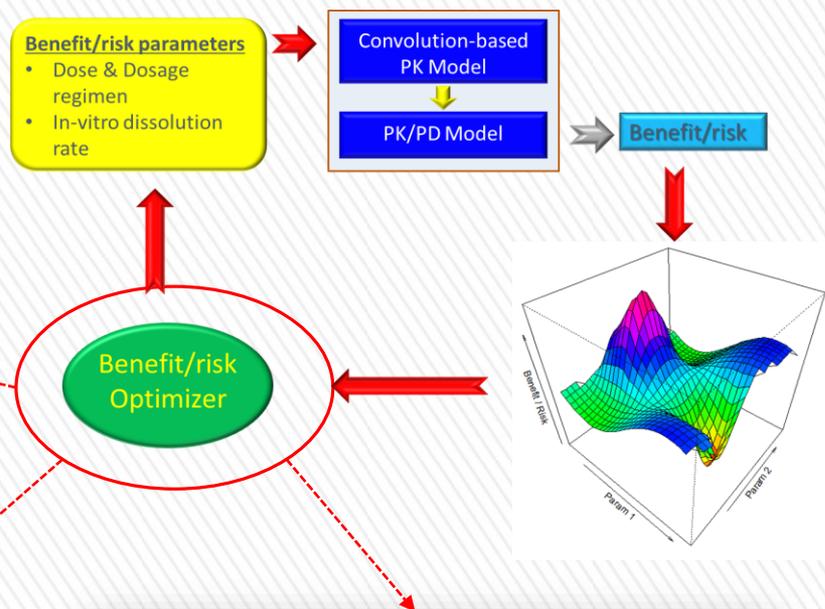
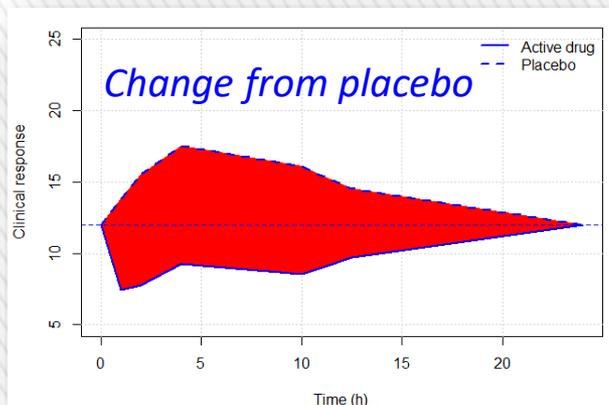
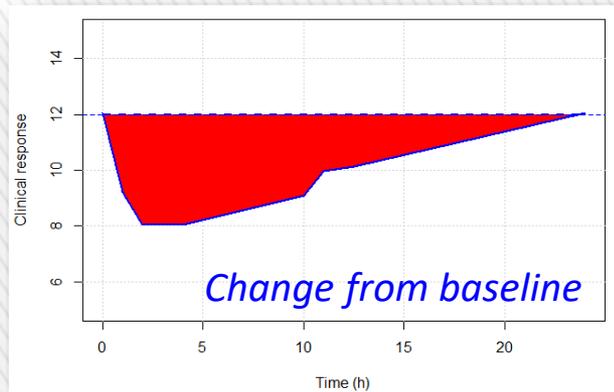


Response Surface Analysis and Nonlinear Optimization Algorithm for Maximization of Clinical Benefit



The optimization process is conducted using the derivative-free non-linear optimization algorithm implemented in the R library NLOPTR (<http://ab-initio.mit.edu/nlopt>)

Clinical Benefit

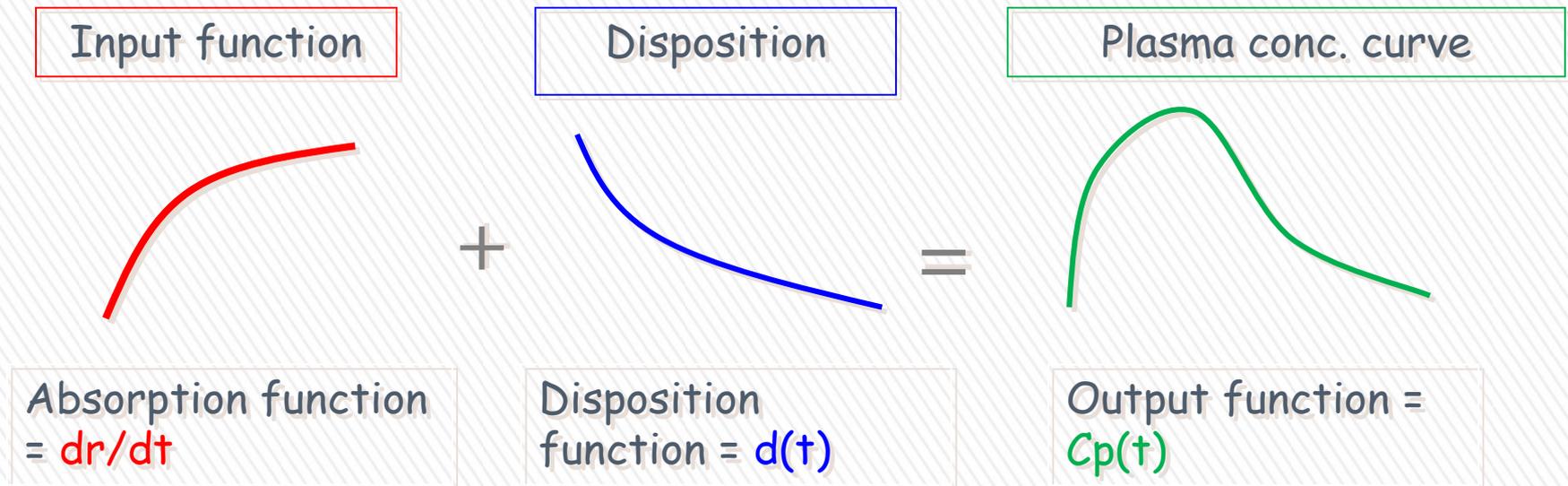


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Convolution integral theory

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

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 $C_p(t)$ 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 (C_p), resulting from an arbitrary dose, can be described by convolution as:

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

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 $C_p(t)$ can be written as

$$\frac{dC_p}{dt} = \text{Dose} \cdot \frac{dr}{dt} - K_{el} \cdot C_p$$

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)

Example of Convolution-based model

in case of a simple *in-vivo* absorption and *in-vivo* disposition (i.e., one compartment), the convolution-based model describing $C_p(t)$ can be written as:

- *in-vivo* absorption, first order rate :

$$r(t) = \text{Dose} \cdot (1 - e^{-k_a \cdot t})$$

where k_a is the first order absorption rate constant

- PK disposition, one compartment with first order elimination rate:

$$\frac{dA}{dt} = -k_{el} \cdot A$$

- Convolution model:

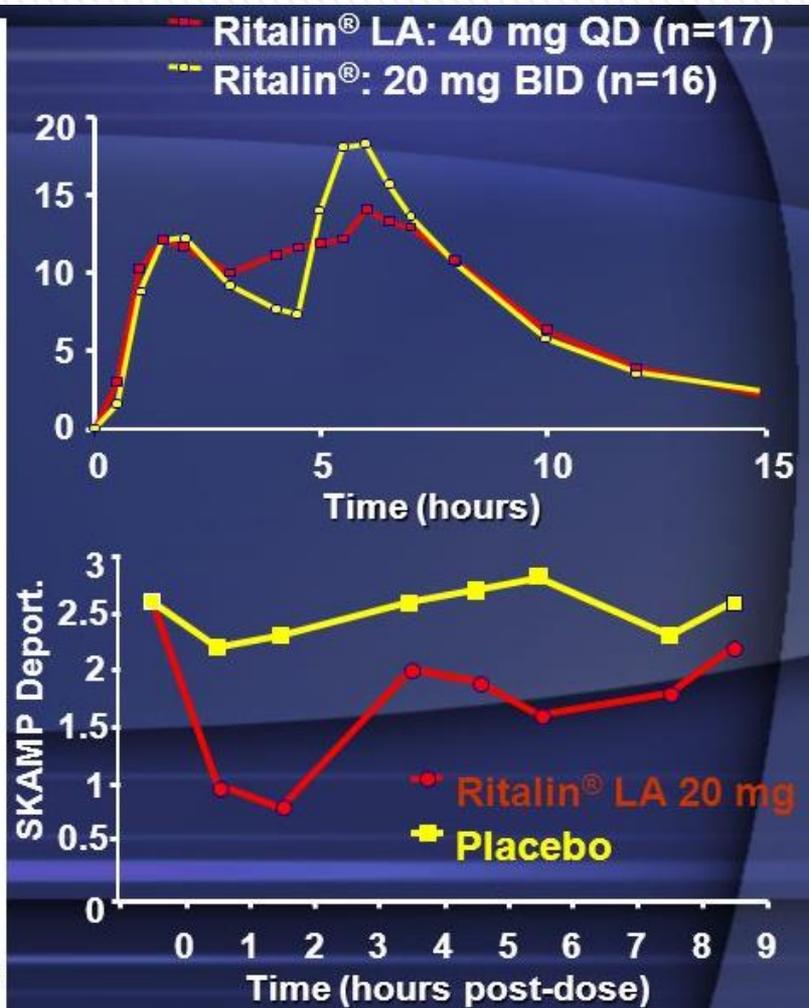
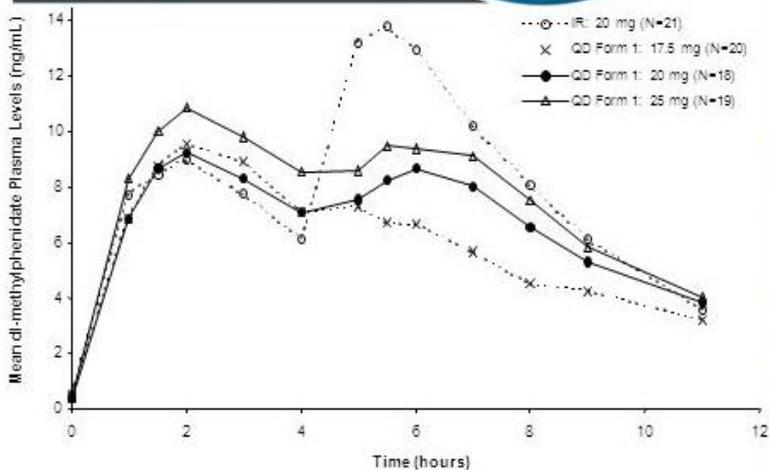
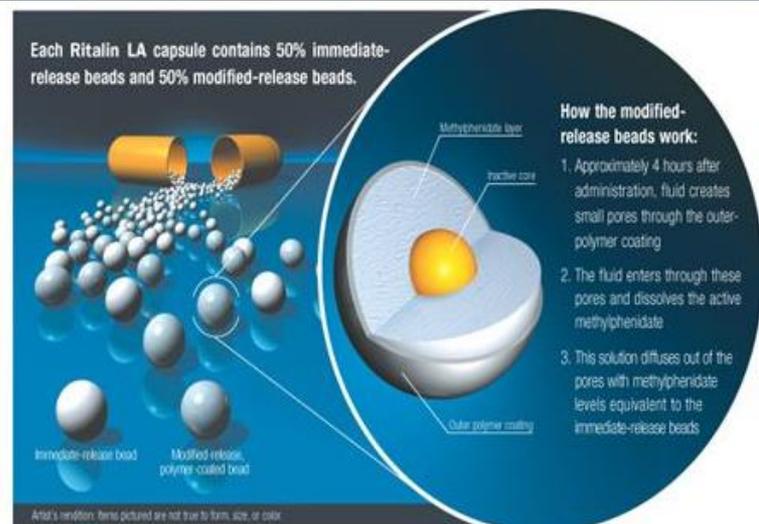
the *in-vivo* drug delivery rate $\frac{dr}{dt}$ can be computed by numerical approximation or by analytical solution as:

$$\frac{dr_{\text{vivo}}}{dt} \cong \frac{r_{\text{vitro}}(t) - r_{\text{vitro}}(t + \Delta)}{\Delta} = \text{Dose} \cdot k_a \cdot e^{-k_a \cdot t}$$

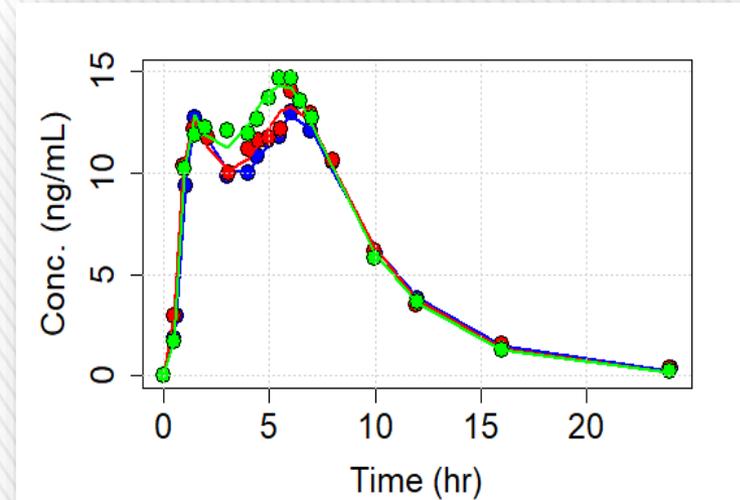
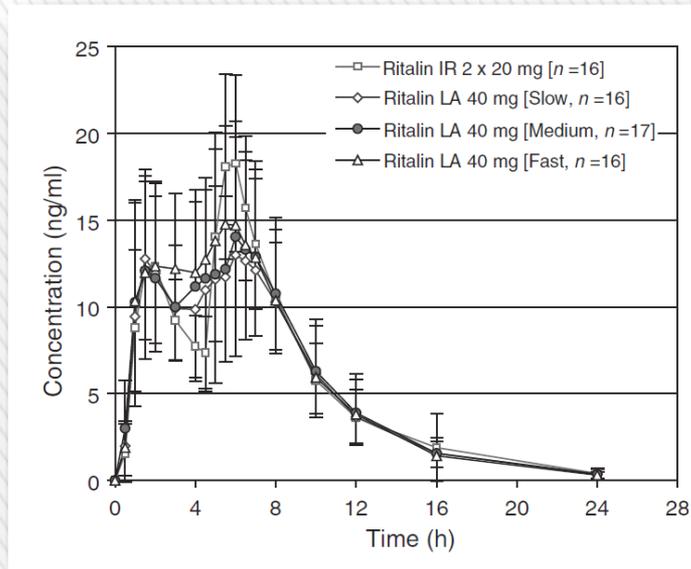
$$\frac{dA}{dt} = \frac{dr}{dt} - k_{el} \cdot A = F \cdot \text{Dose} \cdot k_a \cdot e^{-k_a \cdot t} - k_{el} \cdot A; \quad C_p = \frac{A}{V}$$

Ritalin LA[®] bimodal MPH release for the treatment of ADHD

Ritalin LA[®] uses the proprietary SODAS[®] (Spheroidal Oral Drug Absorption System) technology

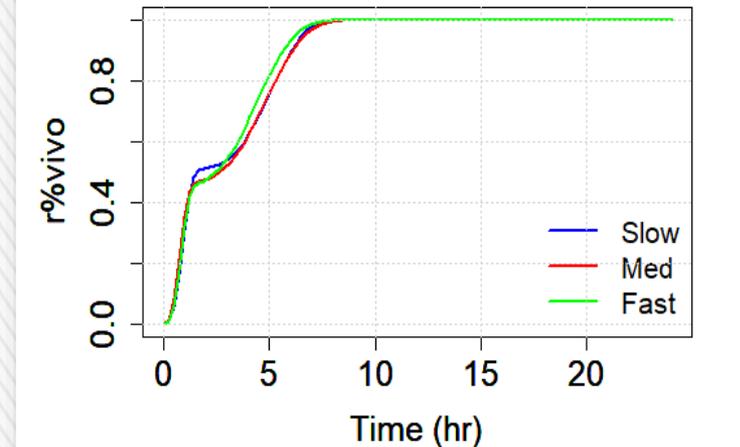


Modeling complex absorption



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

- ff = 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 = sigmoidicity factor for the 1st process
- ss1 = sigmoidicity factor for the 2nd process



$$\frac{dA}{dt} = F \cdot \text{Dose} \cdot \frac{dr}{dt} - k_{el} \cdot A \quad C_p = \frac{A}{V}$$

IVIVC

Definition

An In-vitro/In-vivo correlation (IVIVC) has been defined by the Food and Drug Administration (FDA) as “a predictive mathematical model describing the relationship between an in-vitro property of a dosage form and an in-vivo response

Purpose

- Substitute for additional in vivo experiments (under certain conditions)
- Optimization of formulation
- Scale up post approval changes (Time and cost saving during the product development)
- Surrogate for in vivo bioequivalence

Going beyond the traditional view: IVIVC as a tool for optimizing the clinical benefit of a treatment (CB)

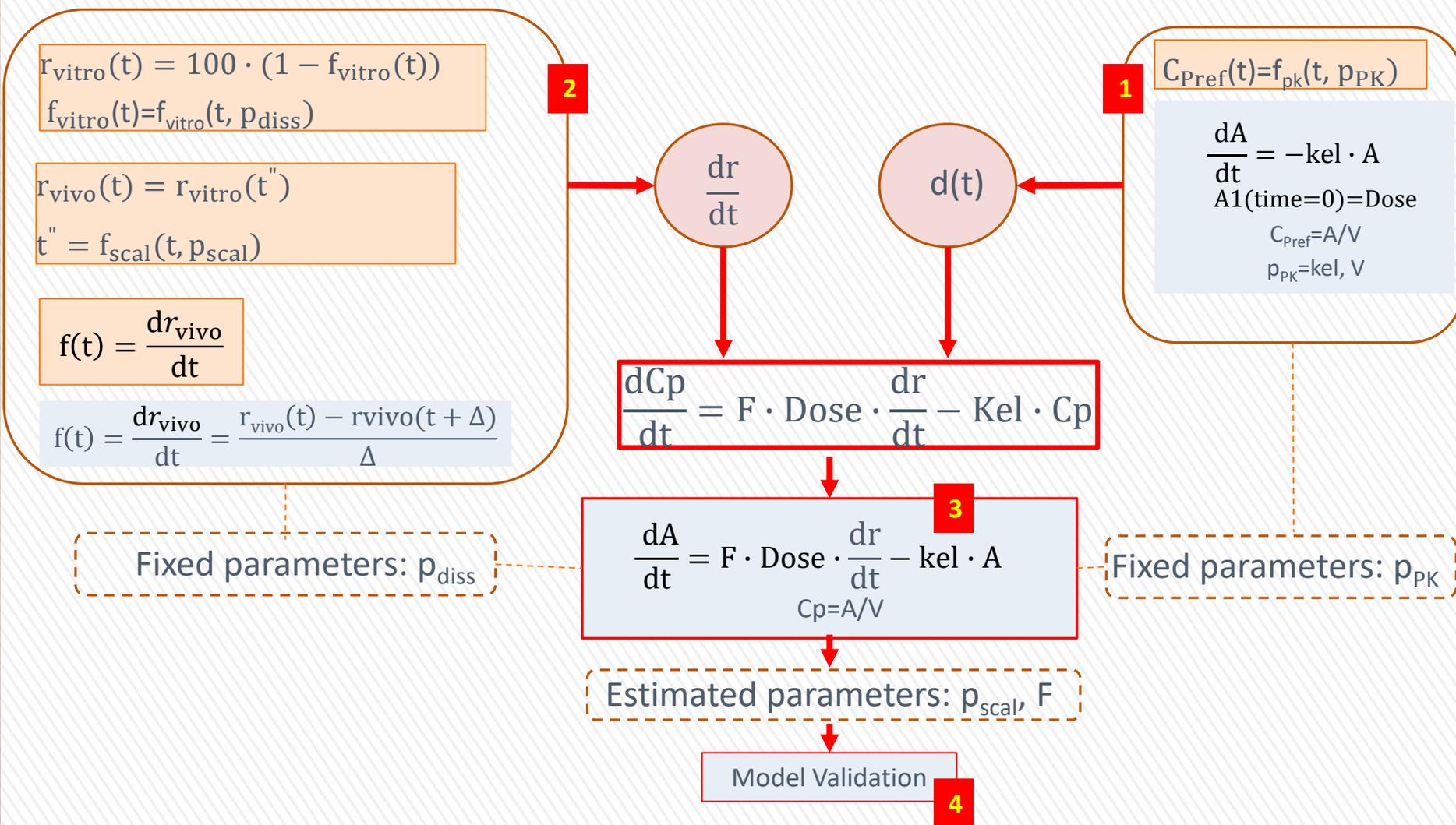
The CB optimization can be achieved by identifying the best performing dose, and dosage regimen jointly with the best performing *in-vivo* release properties of a drug.

The key components of this convolution-based modelling approach * are:

- Assessment of the *in-vivo/in-vitro* correlation (IVIVC),
- Characterization of the drug pharmacokinetics (PK),
- Linking drug exposure and pharmacological response accounting for the placebo effect (PK/PD),
- Identification of the optimal dose and the optimal *in-vivo* drug release properties appropriate for maximizing the CB.

* 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.

Implementing IVIVC using a convolution-based modelling approach



Assessing IVIVC using a convolution-based modelling approach

The IVIVC analysis was conducted using a 4-step approach :

1. Fit the mean PK time-course of the IR formulation (**Step 1**);
2. Individually fit the mean *in-vitro* dissolution data of the slow, medium, and fast formulations using the release function ($r(t)$) (**Step 2**);
3. Evaluate IVIVC by jointly applying the convolution model to the *in-vivo* data of the slow, medium, and fast formulations (**Step 3**) and by:
 - Fixing the *in-vivo* drug release parameters for each formulation to the values estimated in Step (2)
 - Estimating the time scaling factors common to all formulations
4. Evaluate the internal predictability by comparing the predicted (estimated in Step 3) C_{max} , AUC_{inf} , $pAUC_{0-3}$, $pAUC_{3-7}$, and $pAUC_{7-12}$ with the observed values (**Step 4**).

Ritalin LA[®] IVIVC study

The objective of this study was to evaluate the in vitro dissolution and in vivo absorption of d,l-threo-methylphenidate (MPH) from a novel bimodal release formulation (Ritalin[®] LA capsule) compared with an immediate-release formulation (Ritalin IR tablet) in healthy volunteers.

This was a four-treatment, four-period, single dose, randomized crossover study. 16 subjects were retained for the final PK analysis. The subjects received four treatments, after at least a ten h fast, three Ritalin LA capsule formulations (40 mg) and Ritalin IR tablets (two 20 mg given 4h apart) as the reference. The three Ritalin LA formulations were selected to provide slow-, medium- and fast-release in vitro dissolution rates, respectively.

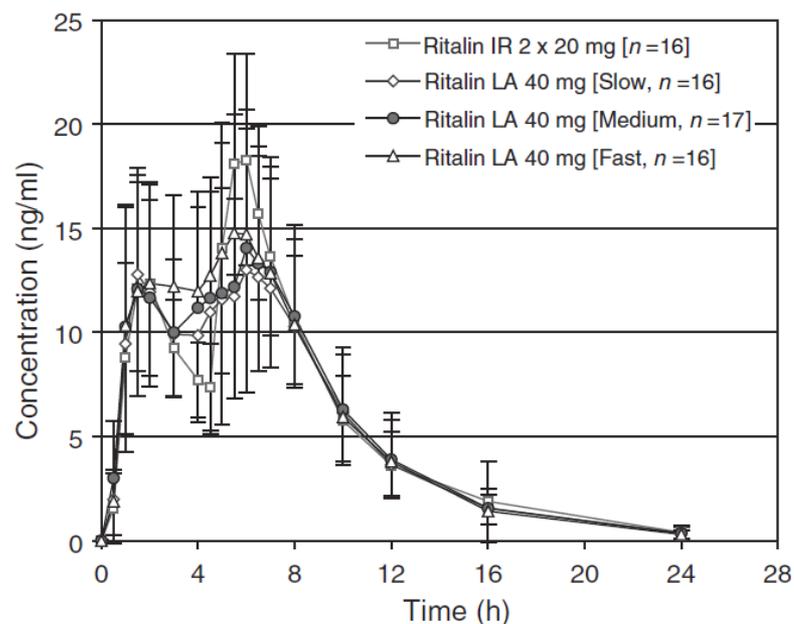


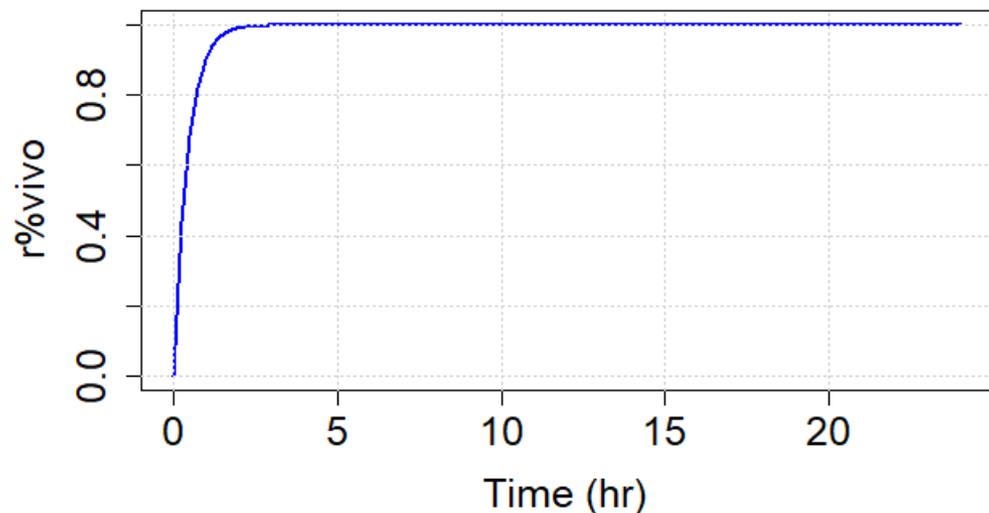
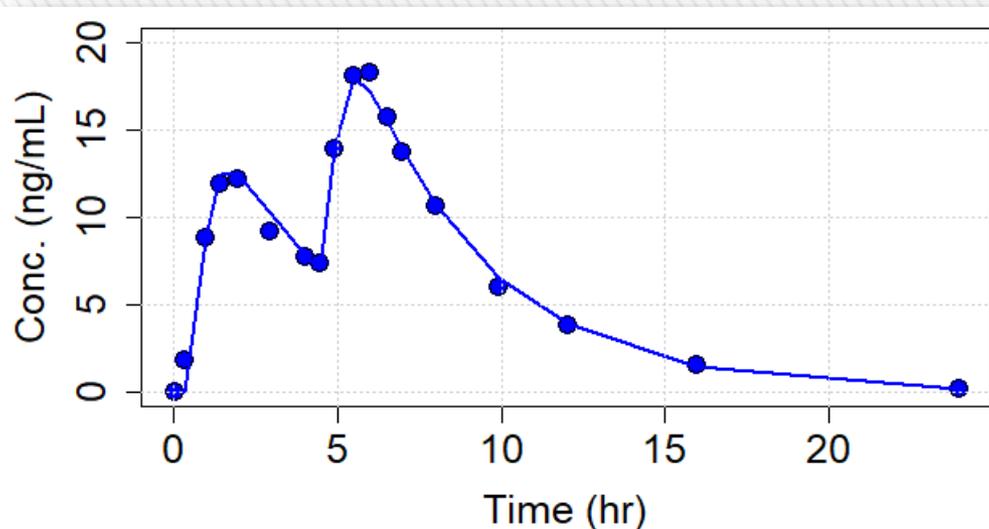
Figure 1. Plasma concentration (mean \pm SD)-time profile of MPH after a single dose of Ritalin LA slow-, medium- or fast-release formulation and Ritalin tablets (immediate release formulation) given 4 h apart

Step 1: Estimate the disposition and the elimination of Ritalin IR

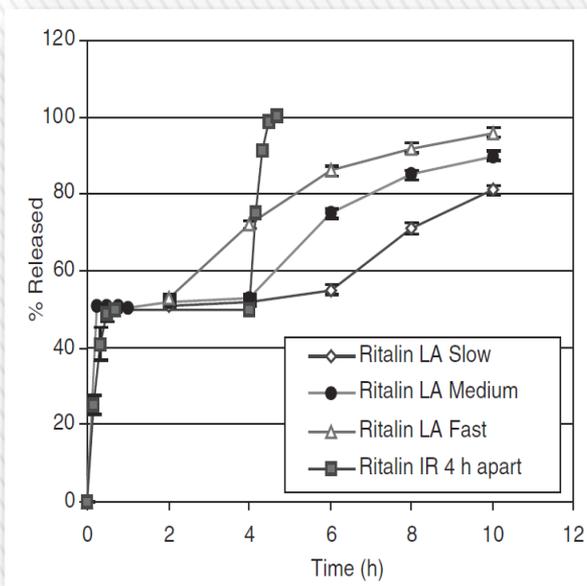
The PK data of Ritalin IR tablets (two 20 mg given four h apart) were considered as the reference and used to estimate the disposition (V) and elimination parameters (k_{el}) of Ritalin

Parameter	Value
$k_a(\text{hr}^{-1})$	2.390
$k_{el}(\text{hr}^{-1})$	0.254
$V(\text{L})$	1.200
Lag(hr)	0.633

The value of volume ($=1.20$ L) and elimination rate k_{el} ($=0.254$ hr^{-1}) were fixed in the assessment of the IVIVC



Step 2: Modelling the in-vitro dissolution data



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

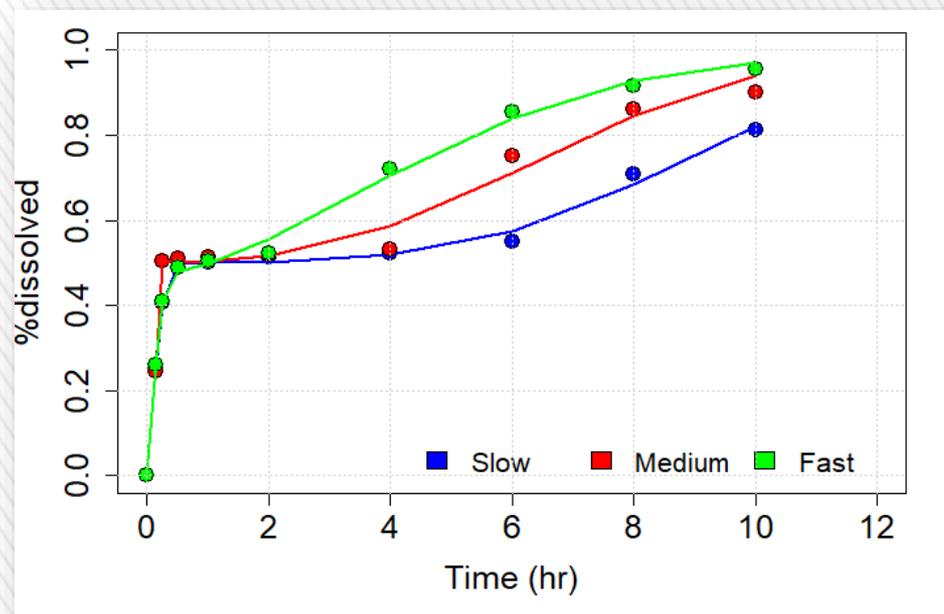
$r(t)$ = % dissolved data

$ff, 1-ff$ = fraction of the drug in the rapid and slow dissolution phases

$ss, ss1$ = shaping factors

$td1, td2$ = time to absorb about 63% in the two dissolution phases

Parameter	Slow	Medium	Fast
td(hr)	0.19	0.16	0.17
ss	1.70	6.55	1.79
td1(hr)	9.91	7.55	5.42
ss1	3.59	2.63	1.75
ff(%)	0.50	0.50	0.47



Time scaling

In a linear correlation, the *in-vitro* dissolution and *in-vivo* input curves may be directly super-imposable or may be made to be super-imposable by the use of a “scaling factor”

A general model for time-scaling model for the IVIVC assessment was used (*)

$$r_{vivo}(t) = a_1 + a_2 \cdot r_{vitro}(tt)$$

$$tt = b_1 + b_2 \cdot t^{b_3}$$

In case of absence of time scaling between r_{vivo} and r_{vitro} :

$$a_1 = 0, a_2 = 1, b_1 = 0, b_2 = 1, \text{ and } b_3 = 1.$$

Otherwise, the values of the parameters a_1 , a_2 , b_1 , b_2 , and b_3 time scaling can be estimated in the IVIVC modeling step the appropriate. The model includes a linear component (intercept of a_1 and slope of a_2), and a nonlinear component describing the time-shifting (b_1), time-scaling (b_2), and time-shaping factor (b_3).

Step 3: Modelling the IVIVC

Principle: predict the $C_p(t)$ values and the in-vivo bioavailability (F) by using the in-vitro time-scaled $[r(t)]$ data and by fixing in this prediction the K_{el} and V values to the values estimated in the analysis of the IR data

$$\frac{dC_p}{dt} = F \cdot Dose \cdot \frac{dr_{vivo}}{dt} - K_{el} \cdot C_p$$

Fixed from in-vitro data

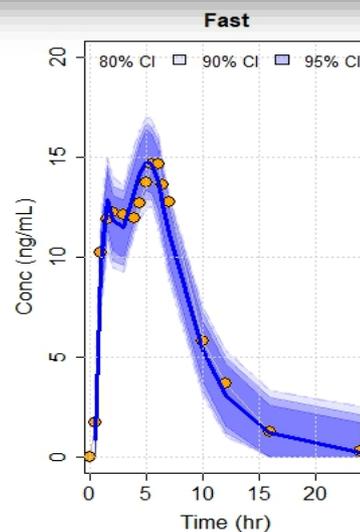
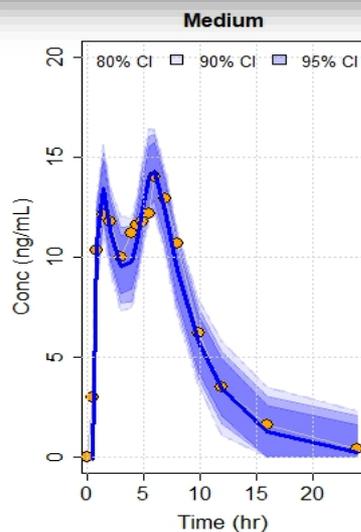
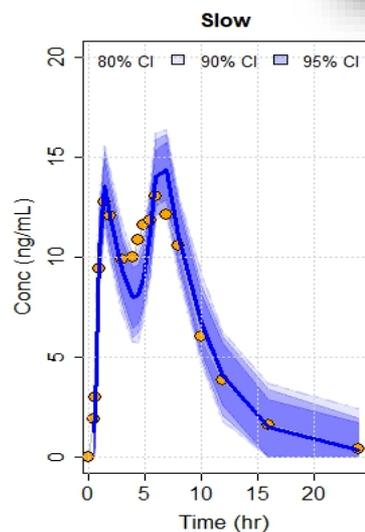
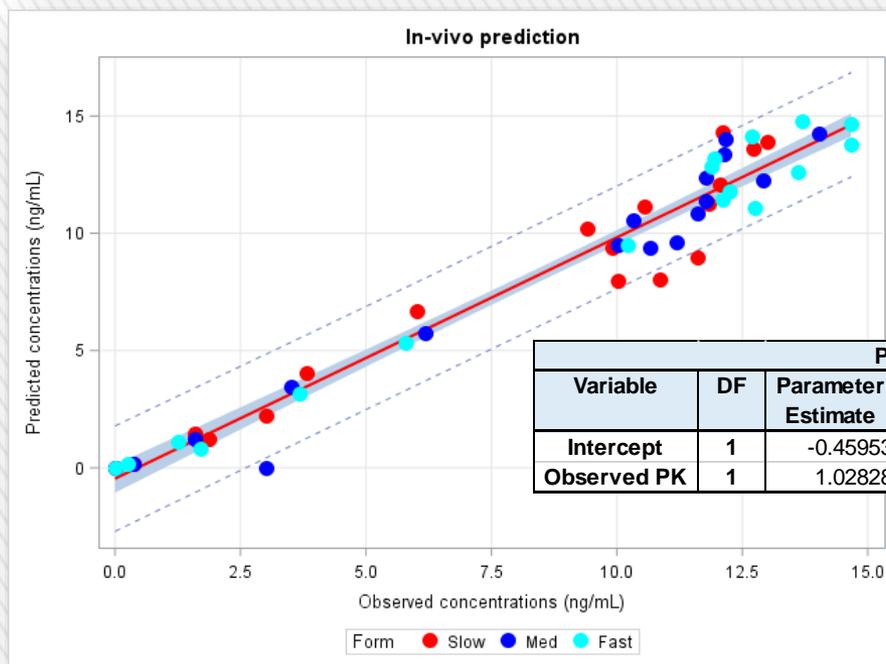
Fixed from IR data

$$r_{vivo}(t) = A_1 + A_2 \cdot r_{vitro}(tt); \quad tt = B_1 + B_2 \cdot t^{B_3}$$

Time scaling and bioavailability parameter values estimated in the IVIVC analysis

Parameter	Value	FIX	SE	RSE
A1	0	FIX	0	0%
A2	1	FIX	0	0%
B1	0	FIX	0	0%
B2	0.19	-	0.002	1.20%
B3	2.24	-	0.053	2.40%
F	0.94	-	0.018	1.90%
err_add	1.13	-	0.099	8.80%
OFV=61.402				

Step 3: Evaluating the IVIVC



Mean PK observed concentrations (orange dots) with the predicted values by the convolution model (blue solid lines) by formulation. The shaded areas represents the 80%, 90%, and 95% prediction intervals

Assessing predictability (%PE)

$$\%PE = \frac{1}{n} \sum_{1}^n \frac{|\text{Observed value} - \text{Predicted value}|}{\text{Observed value}} \cdot 100$$

In addition to AUCinf and Cmax, additional metrics based on the concept of partial AUC were considered for the assessment of %PE.

These criteria were based on the recent recommendations of the FDA for using partial AUC (pAUC) metrics for studies conducted in fasting conditions, to assess the bioequivalence of generic ER formulations of MPH*.

The following pAUC were considered:

- *pAUC0-3, AUC from 0 to 3 hours,*
- *pAUC3-7, AUC from 3 to 7 hours,*
- *pAUC7-12, AUC from 7 to 12 hours*

* Food and Drug Administration. Draft Guidance on Methylphenidate Hydrochloride 2015.

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm281454.pdf>

Predictability

$$PE = \frac{1}{n} \sum_1^n \frac{|\text{Obs. value} - \text{Pred. value}|}{\text{Obs. value}} \cdot 100$$

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

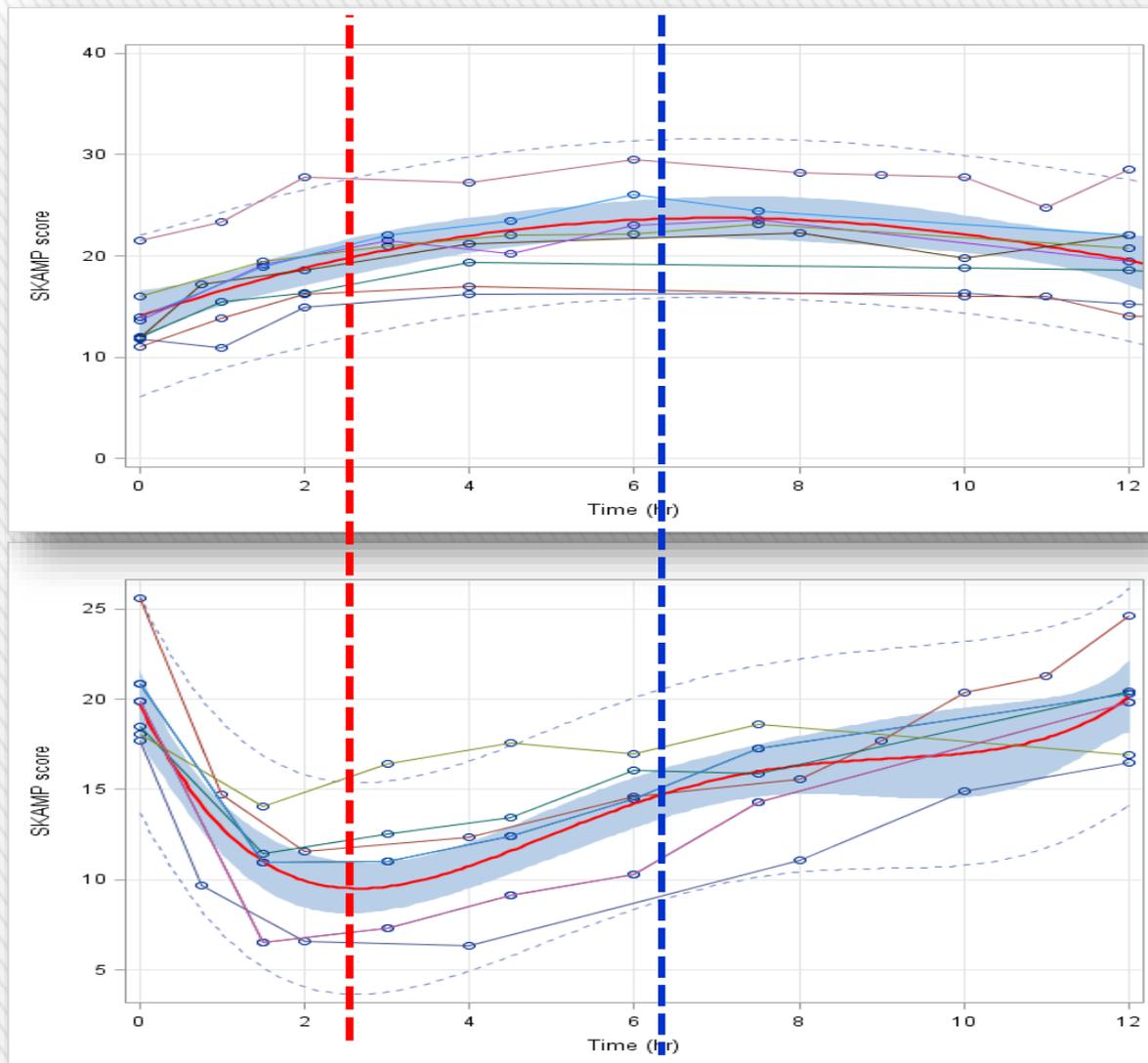
Predictability criteria:

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

0 - 3 hr				3 - 7 hr				7 - 12 hr			
Formulation	auc_o	auc_p	pe_auc	Formulation	auc_o	auc_p	pe_auc	Formulation	auc_o	auc_p	pe_auc
Slow	14.70	15.09	2.62	Slow	44.70	41.71	6.68	Slow	26.25	28.44	8.35
Medium	16.99	16.30	4.05	Medium	46.70	46.15	1.18	Medium	25.96	23.80	8.36
Fast	15.18	14.79	2.62	Fast	45.96	47.16	2.62	Fast	36.63	32.59	11.03
Average			3.10	Average			3.49	Average			9.24

The highest mean prediction errors is **11.03%** for the individual formulations (<15% max acceptable value) and the highest mean absolute prediction error for the 3 formulations is **9.24 %** for pAUC7-12 (<10% max acceptable value)

Placebo and MPH SKAMP score data

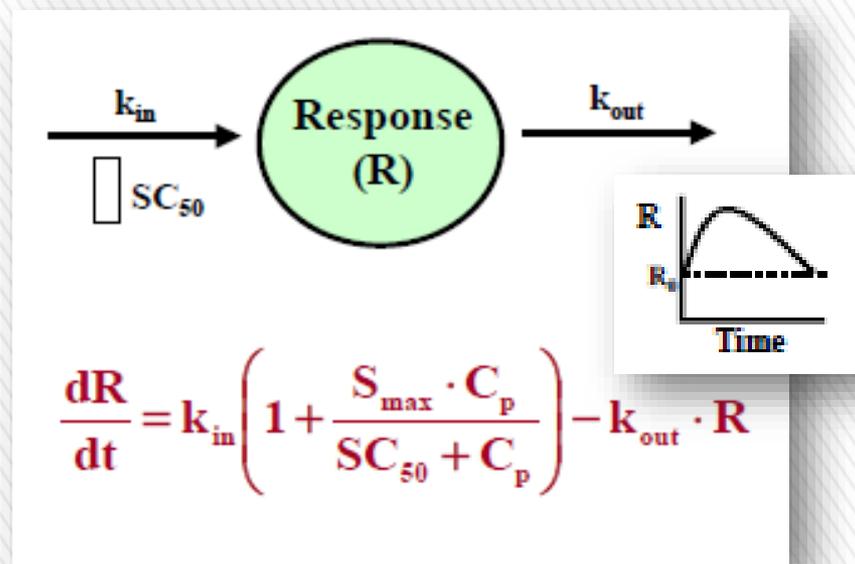


Semi-mechanistic Placebo response model

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 R_0 .

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

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

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

Exposure-response model

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

Where:

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

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

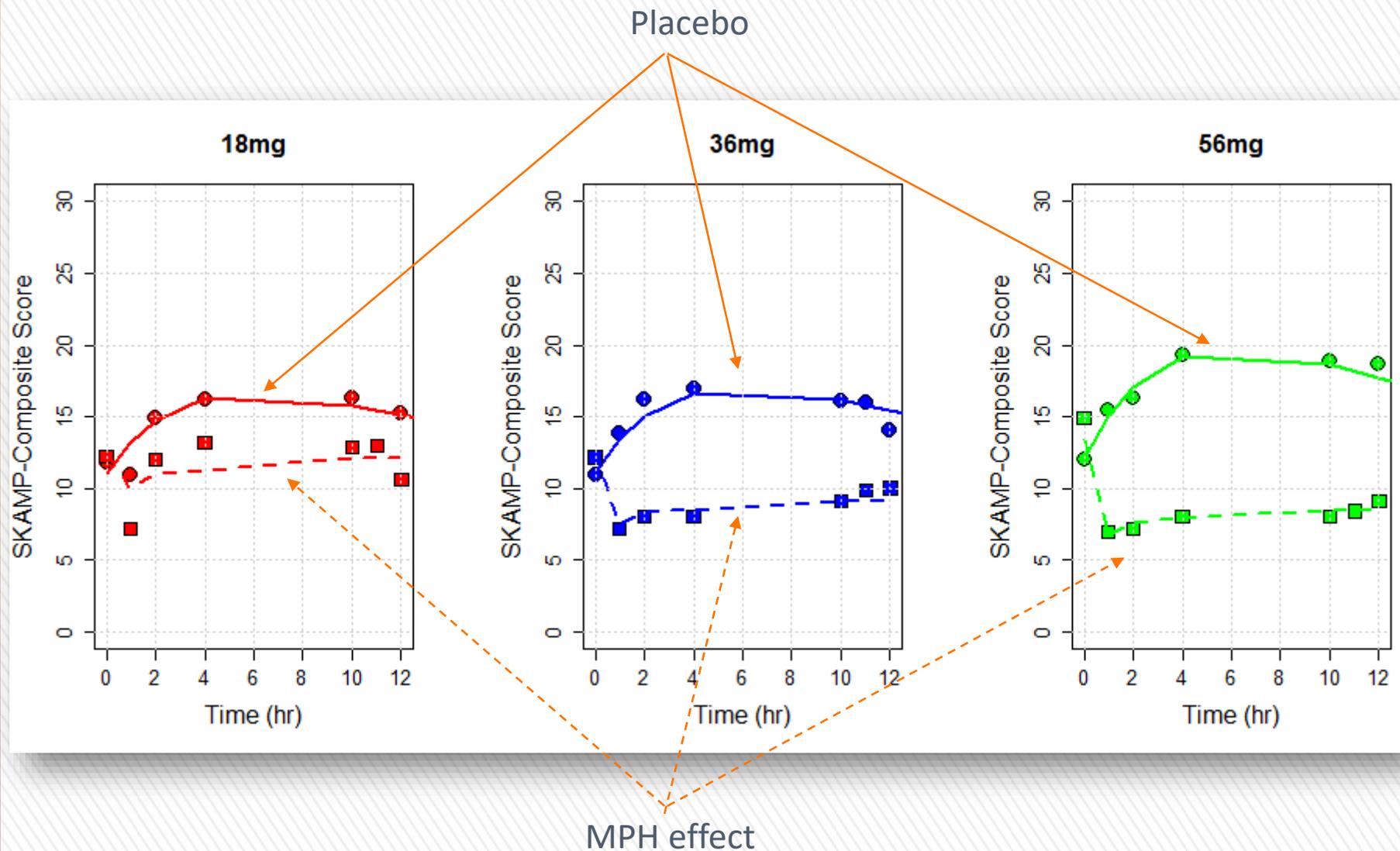
Δ is the score difference at baseline depending on the treatment between assessment days

E_{max} is the maximal MPH related effect

EC_{50} is the MPH concentration associated with 50% of the maximal effect

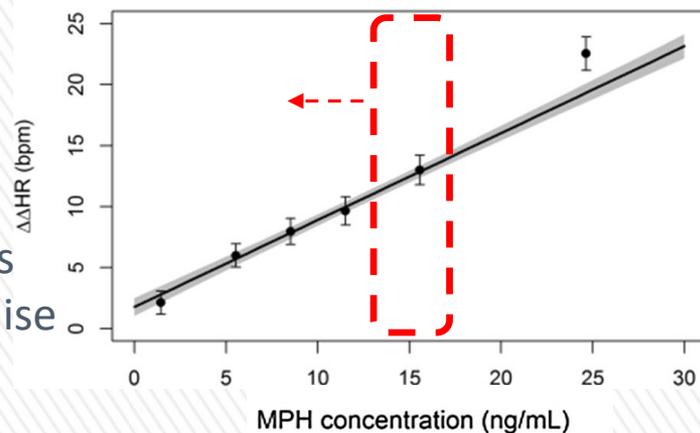
C_p is the MPH drug concentration

The PK/PD model – Effect of MPH on the SKAMP clinical scores

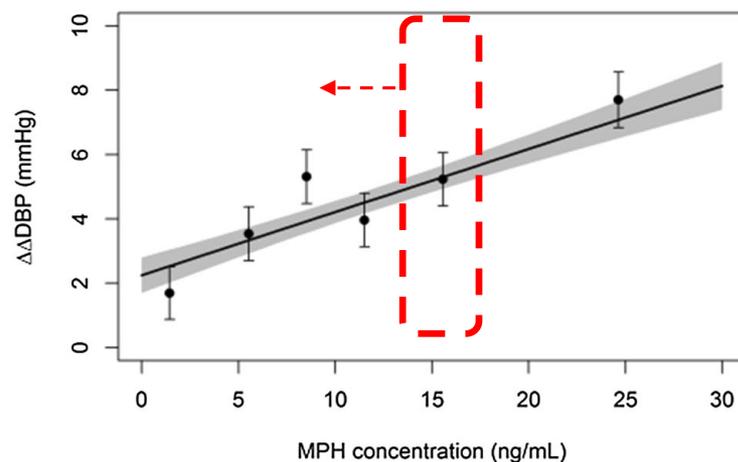
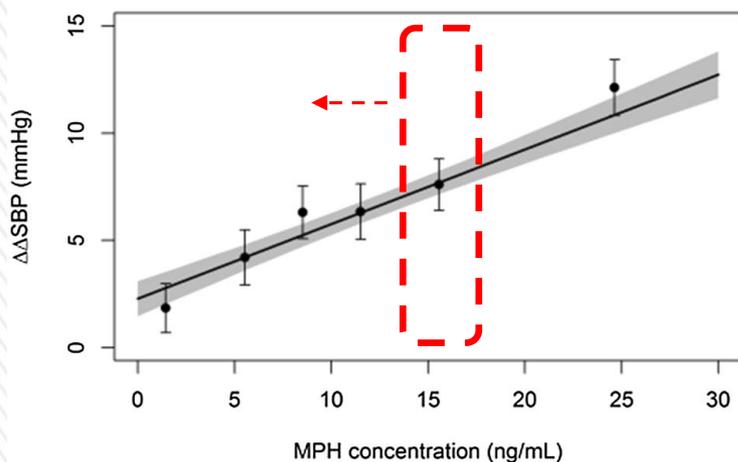


Exposure–response analyses of blood pressure and heart rate changes for methylphenidate in healthy adults

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.



40 mg



Li L, Wang Y, Upoor 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.

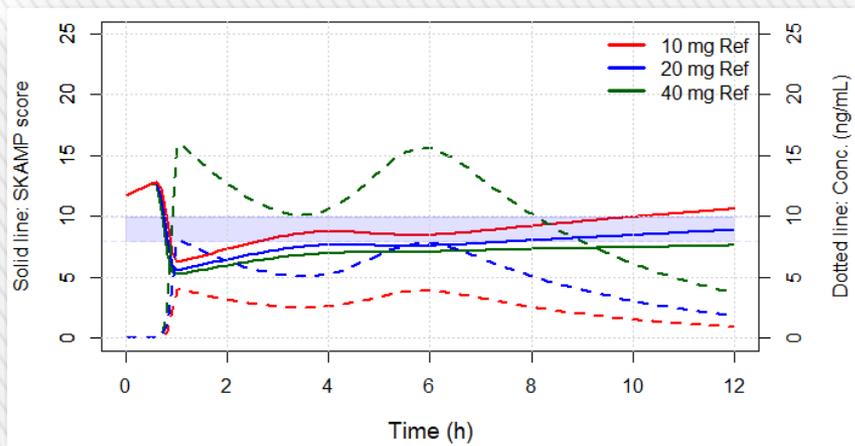
Clinical benefit

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

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

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

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

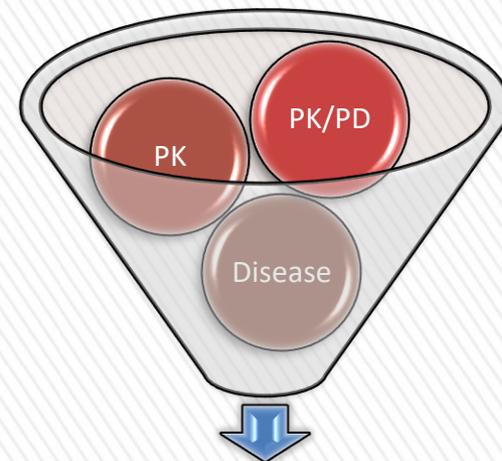


CB: maintenance of SKAMP scores from 8 to 10 during 12 hours was considered as the target clinical response

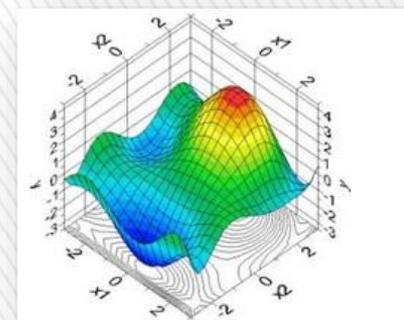
$$CB = f(SKAMP)$$

$$SKAMP = f(Cp)$$

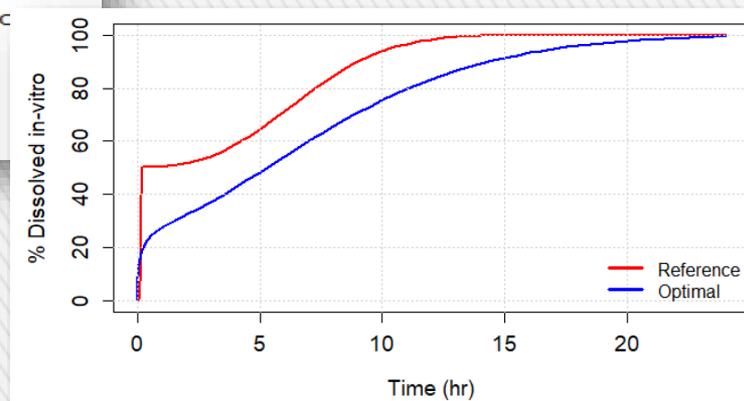
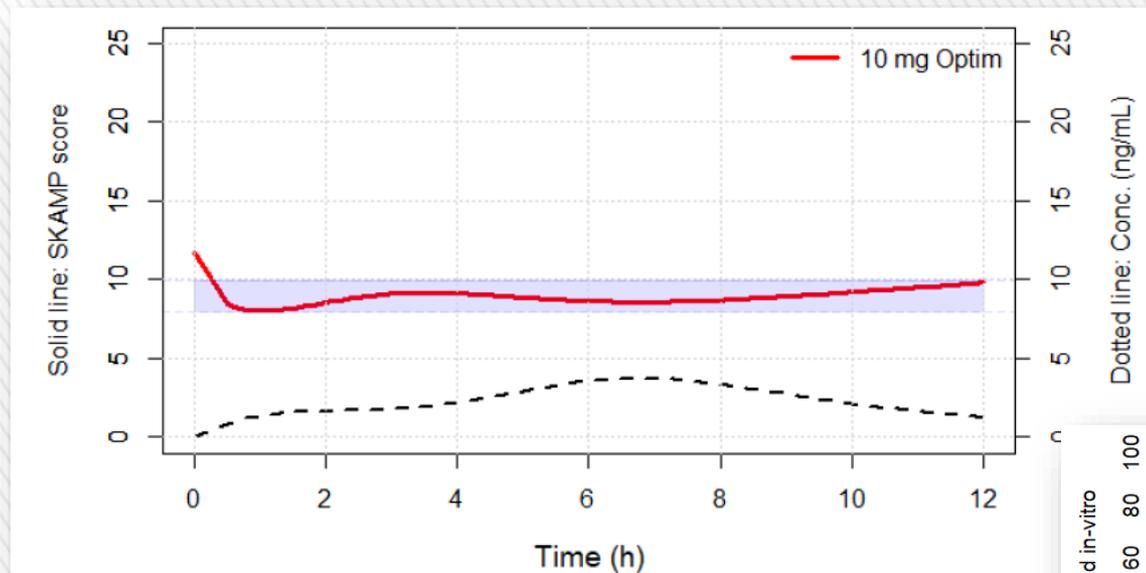
$$Cp(ff, ss, ss1, td, td1, Dose)$$



Response variable = Clinical benefit



Optimized response



	TD (hr)	SS (unitles)	SS1 (unitles)	TD1 (hr)	FF (%)	DOSE (mg)	Cmax (ng/mL)
Reference	0.16	6.55	2.63	7.55	0.50	40	15.85
Optimized	0.17	0.53	1.68	9.58	0.28	10	3.73

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.

Thank you

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