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IVIVC current status and future perspectives

LAI 2019 conference

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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)

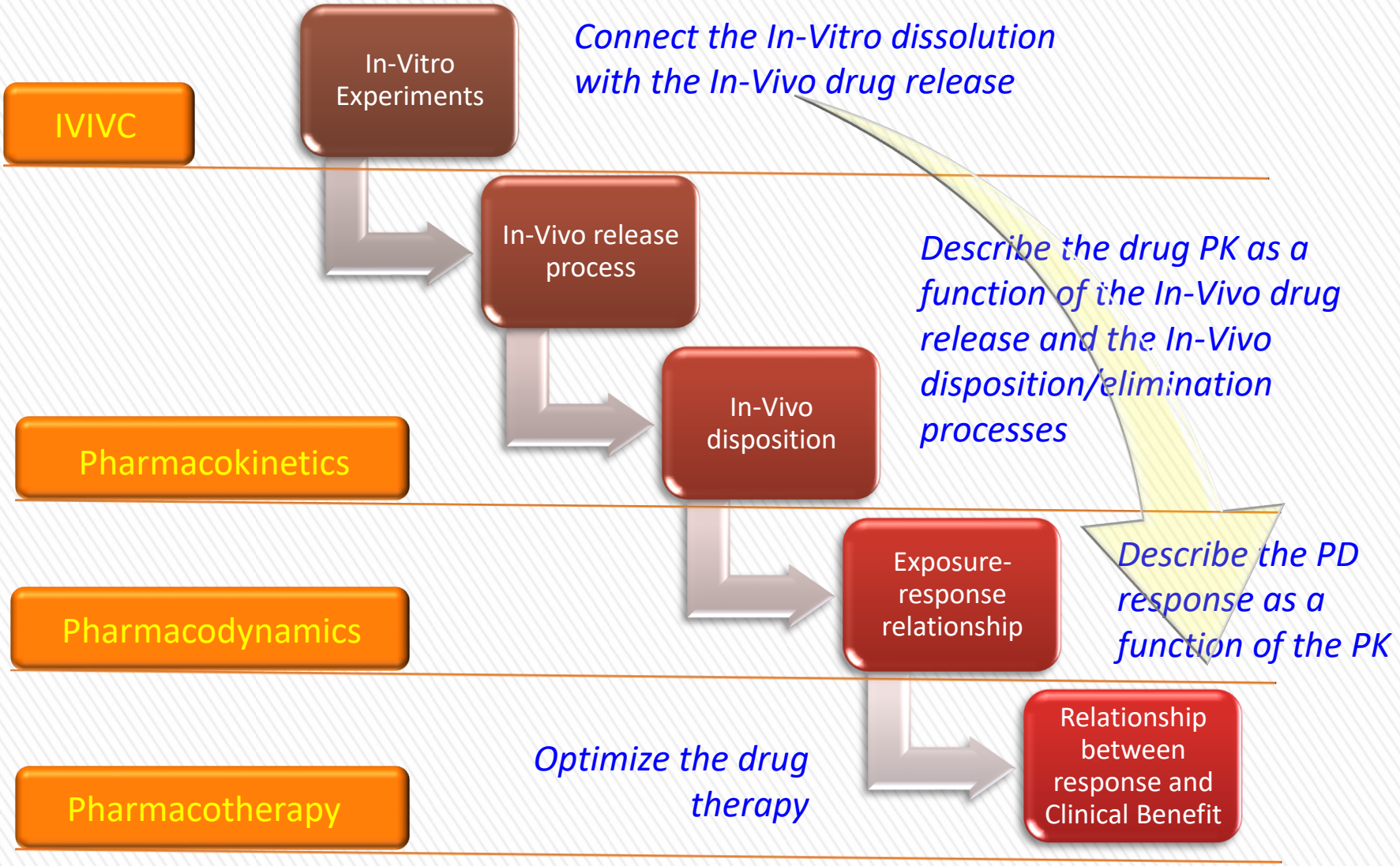
The CB optimization can be achieved by identifying the best performing dose, and dosage regimen jointly with the best performing *in-vivo* release properties of a drug.

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.*

Modelling components



* 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.

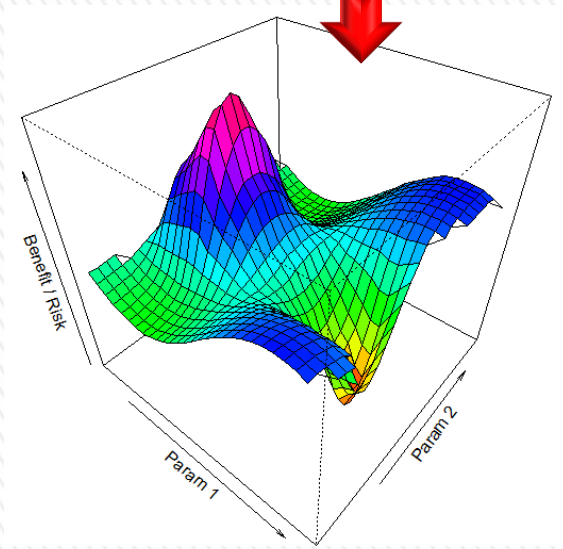
Response Surface Analysis and Nonlinear Optimization Algorithm for Maximization of Clinical Benefit

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

Convolution-based PK Model

PK/PD Model

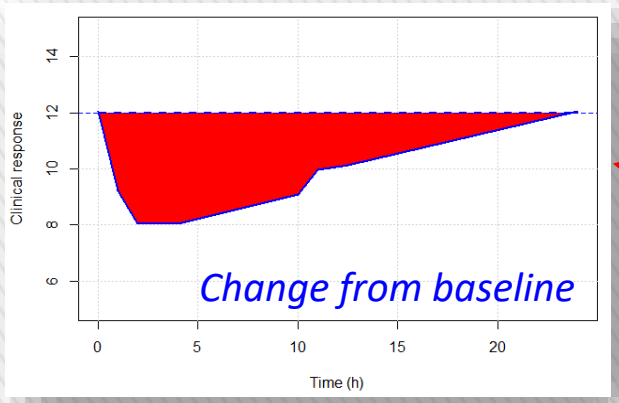
Benefit/risk

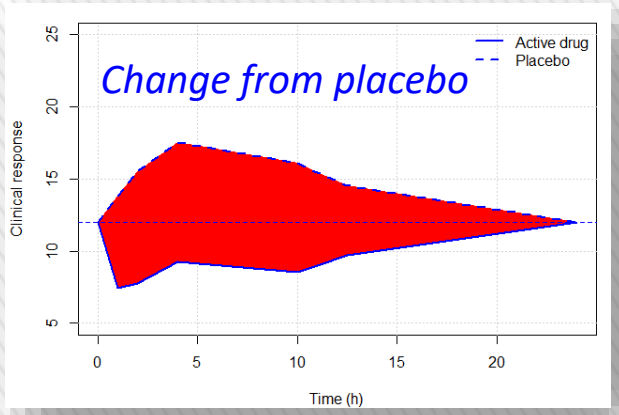


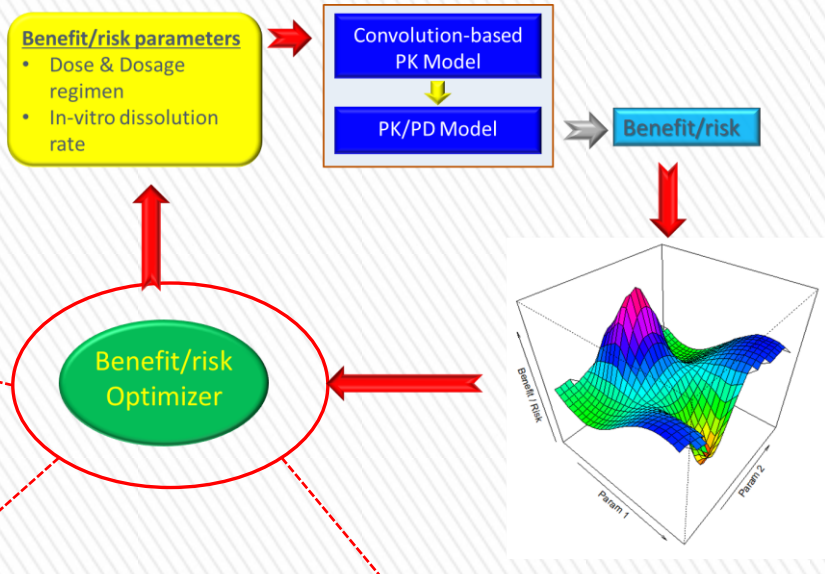
Benefit/risk Optimizer

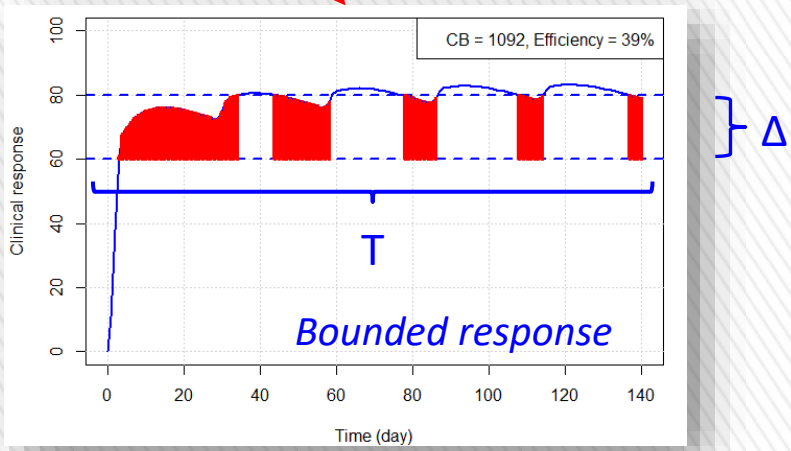
The optimization process is conducted using the derivative-free non-linear optimization algorithm implemented in the R library NLOPTR (http://ab-initio.mit.edu/nlopt)

Clinical Benefit









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:

$$C_p(t) = f(t) * d(t)$$

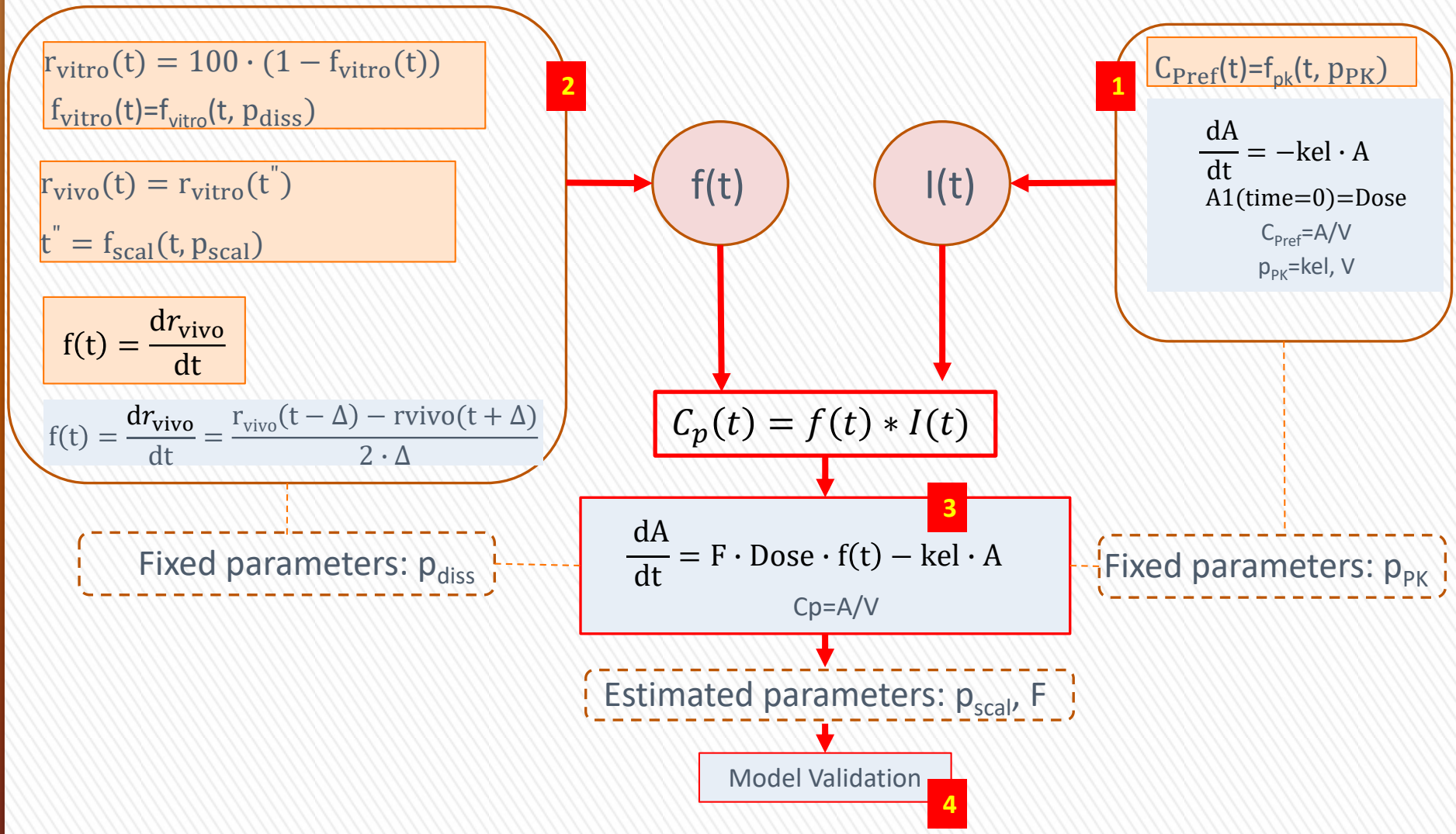
where f(t) is the rate of in-vivo drug delivery, d(t) is the unit impulse response and * is the symbol defining the convolution.

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

$$\frac{dCp}{dt} = f(t) - K \cdot C \qquad \text{where} \qquad f(t) = \frac{dr}{dt}$$

Assuming that the time-varying fraction of the dose released can be described by the function r(t) (input function), we can solve the previous equation by estimating f(t) as the first derivative of r(t) . This can be computed analytically or can be approximated using the finite difference approach (see an example of implementation in NONMEM)

Implementing IVIVC using a convolution-based modelling approach



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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) Cmax, AUCinf, pAUC0-3, pAUC3-7, and pAUC7-12 with the observed values (Step 4).

Example of Convolution-based model

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

- *in-vitro* dissolution, constant dissolution rate:

$$r_{vitro} = Dose \cdot (1 - e^{-k_a \cdot t})$$

where k_a is the first order absorption rate constant

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

$$\frac{dA}{dt} = -kel \cdot A$$

with the assumption that $r_{vivo}=r_{vitro}$, the *in-vivo* drug delivery rate is computed (by numerical approximation or by analytical solution) as:

$$f(t) = \frac{dr_{vivo}}{dt} \cong \frac{r_{vitro}(t-\Delta) - r_{vitro}(t+\Delta)}{2 \cdot \Delta} = Dose \cdot k_a \cdot e^{-k_a \cdot t}$$

- Convolution model:

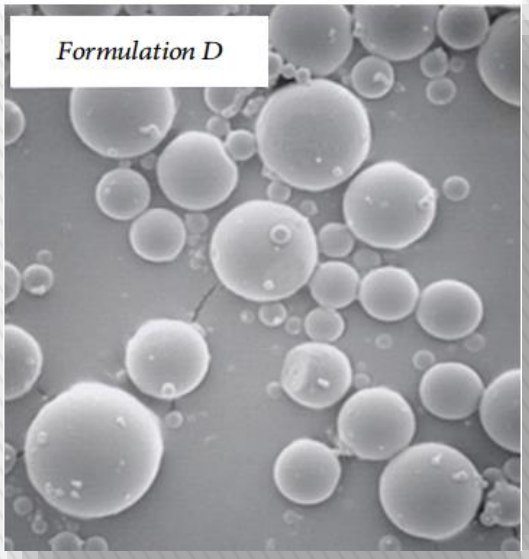
$$\frac{dA}{dt} = f(t) - kel \cdot A = F \cdot Dose \cdot k_a \cdot e^{-k_a \cdot t} - kel \cdot A; \;\; C_p = \frac{A}{V}$$

Case studies

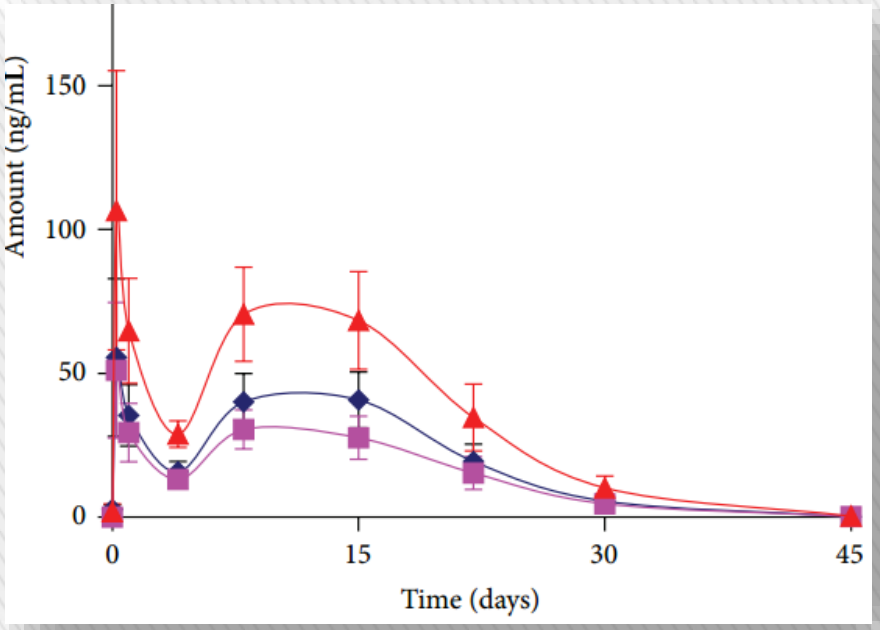
- Use convolution-base modelling for assessing IVIVC for Risperdal® Consta® LAI formulation of risperidone for the treatment of schizophrenia
- Optimize benefit-risk via IVIVC and convolution-based modeling for methylphenidate for the treatment of ADHD

Risperdal® Consta® LAI formulation of risperidone

The objective of this study was to establish IVIVC using the dissolution data of 4 long-acting subcutaneous risperidone formulations and the in-vivo PK measurements. Two copolymers of PLGA (50:50 and 75:25) were used to prepare four microsphere formulations of risperidone, an atypical antipsychotic.



Formulation D: Scanning electron microscopy of Risperidone PLGA microspheres



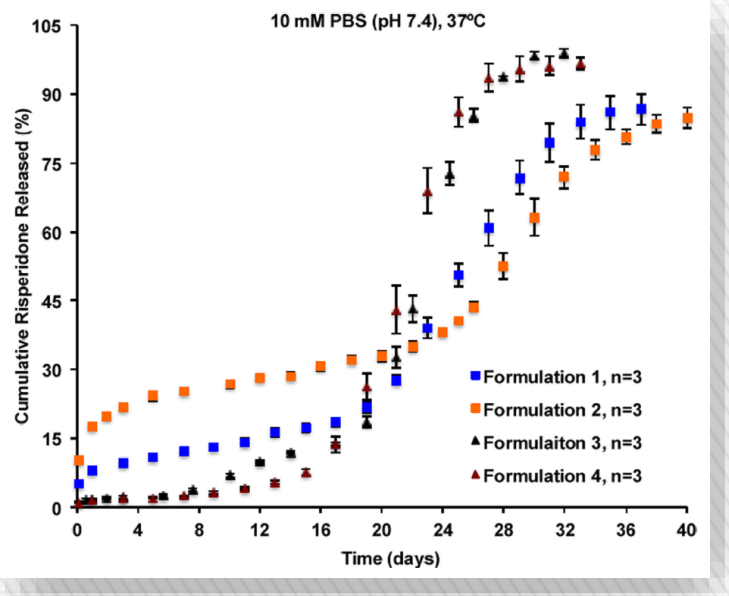
Formulation D: In vivo PK time course

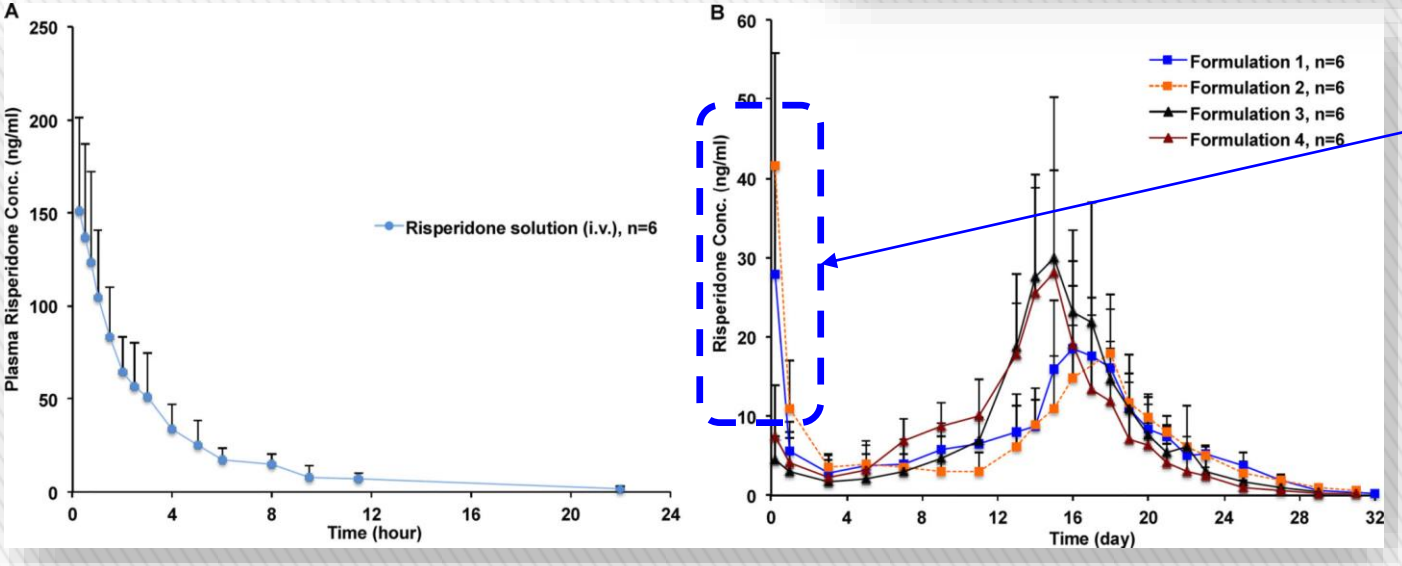
D'Souza S., Faraj J.A., Giovagnoli S., DeLuca P.P..Development of Risperidone PLGA Microspheres. Journal of Drug Delivery. 2014, 620464, 11

Risperdal Consta® - Study design

In vitro release of the risperidone PLGA microspheres was investigated using 4 release testing methods. *In vivo* PK profiles of the risperidone microsphere was evaluated using:

- IV dose of 0.2 mg/kg
- intramuscular administration of the prepared risperidone PLGA microspheres at a dose of 1.92 mg/kg





Shen J, Choi S, Qu W, Wang Y, Burgess DJ. In vitro-in vivo correlation of parenteral risperidone polymeric microspheres. J Control Release. 2015 Nov 28;218:2-12.

Implementing a convolution based model for LAI products

t_1=time-delt

t_2=time+delt

$$abs1 = f \cdot e^{-\left(\left(\frac{t_1}{td}\right)^{ss}\right)} + (1-f) \cdot e^{-\left(\left(\frac{t_1}{td1}\right)^{ss1}\right)}$$

$$abs2 = f \cdot e^{-\left(\left(\frac{t_2}{td}\right)^{ss}\right)} + (1-f) \cdot e^{-\left(\left(\frac{t_2}{td1}\right)^{ss1}\right)}$$

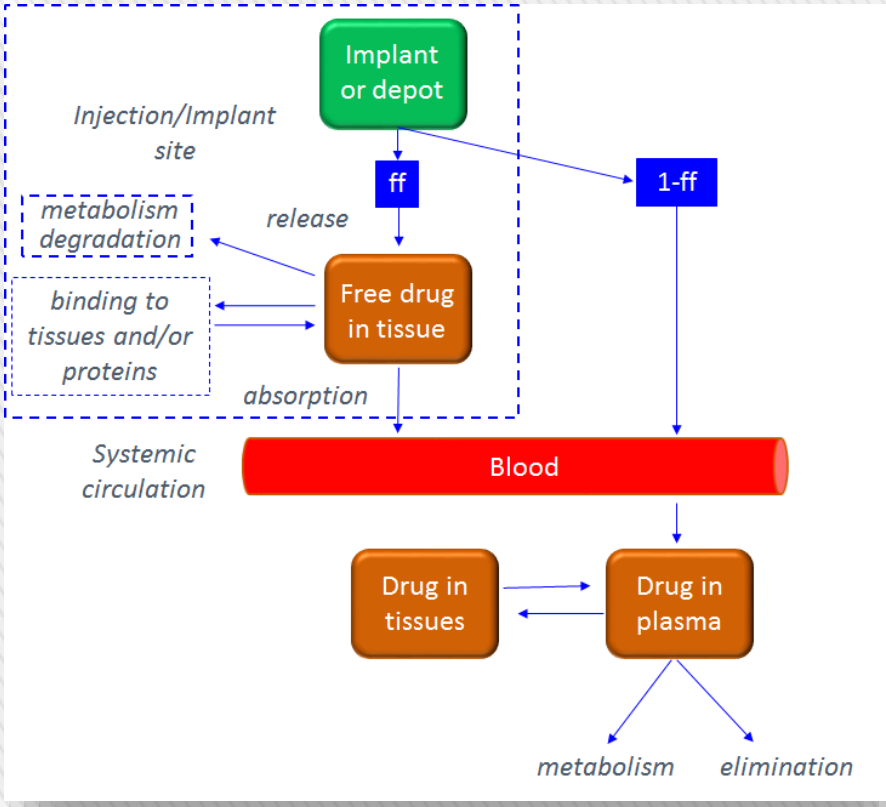
$$kab = \frac{(abs1 + abs2)}{(t_2 - t_1)}$$

$$\frac{dA_1}{dt} = Dose \cdot kab - (kel + k12) \cdot A_1 + k21 \cdot A_2$$

$$\frac{dA_2}{dt} = k12 \cdot A_1 - k21 \cdot A_2$$

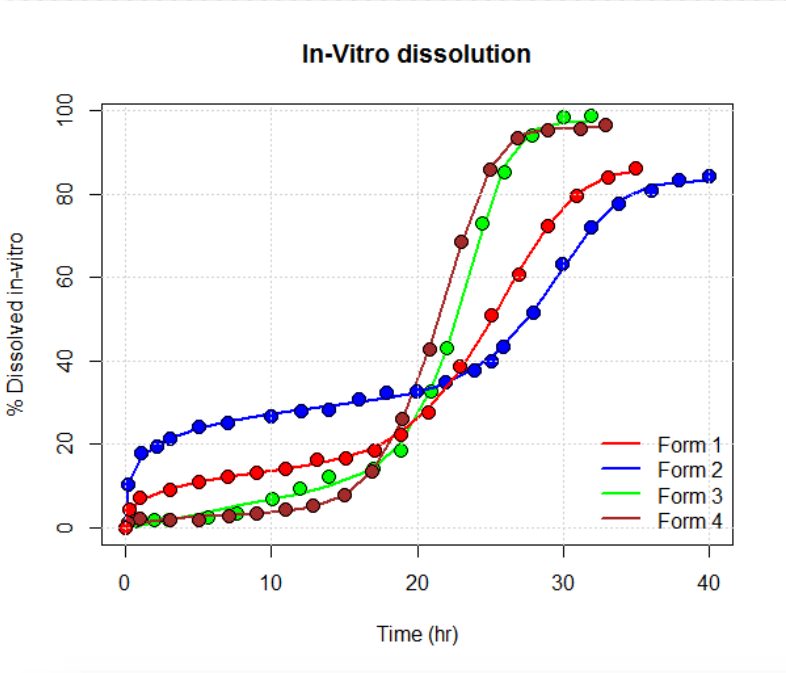
$A_1(time = 0) = ff \cdot Dose$ **[Depot]**

$A_2(time = 0) = (1 - ff) \cdot Dose$ **[Plasma comp]**



Risperdal Consta®: Modelling In-vitro dissolution and IV data

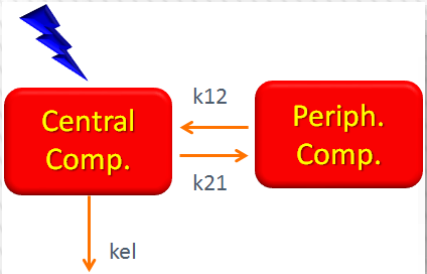
In-Vitro: Double Weibull model



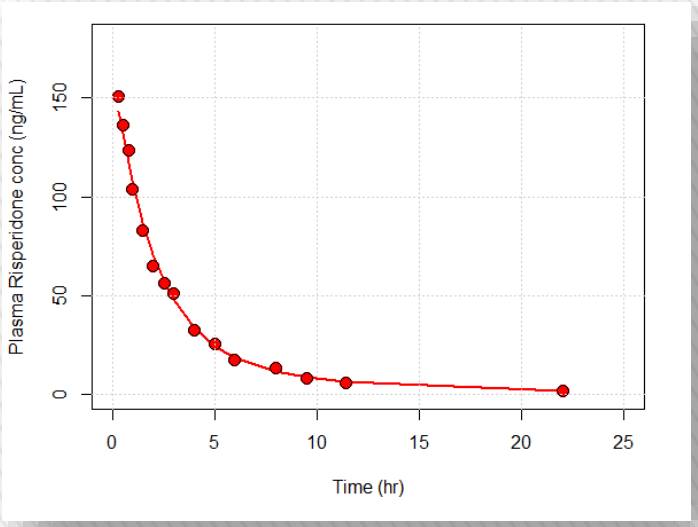
Formulation	TD	SS	TD1	SS1	FF
1	18.02	1.21	23.92	9.35	0.18
2	44.31	0.50	22.47	7.86	0.10
3	26.71	0.29	30.29	8.46	0.52
4	56.11	0.37	26.70	6.45	0.33

$$r_{vitro}(t) = 100 \cdot \left[1 - \left(ff \cdot e^{-\left(\left(\frac{time}{td}\right)^{ss}\right)} + (1-ff) \cdot e^{-\left(\left(\frac{time}{td1}\right)^{ss1}\right)}\right)\right]$$

In-Vivo: Two-compartment model



Parameter	Estimate
KEL	0.34
K12	0.10
K21	0.16
V1	0.61



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 (*)

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

$$tt = b_1 + b_2 \cdot t^{b3}$$

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

$a_1 = 0$, $a_2 = 1$, $b_1 = 0$, $b_2 = 1$, and $b_3 = 1$.

Otherwise, the values of the parameters a1, a2, b1, b2, and b3 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 (b3).

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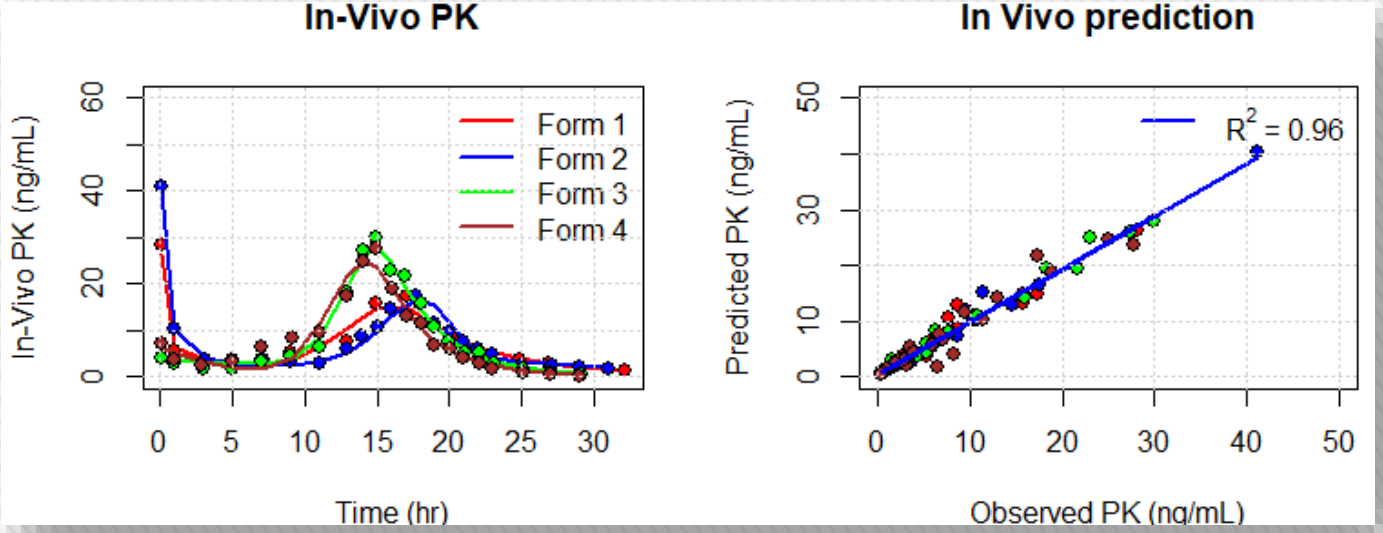
Risperdal Consta®: Modelling IVIVC data



Parameter	Estimate
A1	0.00
B1	1.78
A2	0.14
B2	1.62
B3	1.00
Bioav	0.74
ff	0.99

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

	Observed values		Predicted values		Prediction error	
Formulation	Cmax (ng/mL)	AUC (ng*hr/mL)	Cmax (ng/mL)	AUC (ng*hr/mL)	p_AUC (%)	p_Cmax (%)
1	28.21	207.92	26.28	211.02	1.49	6.84
2	41.11	200.61	40.34	200.46	0.08	1.89
3	29.94	225.91	27.96	232.16	2.77	6.62
4	27.79	215.91	24.81	209.34	3.04	10.73
Average					1.84	6.52

Predictability criteria:

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

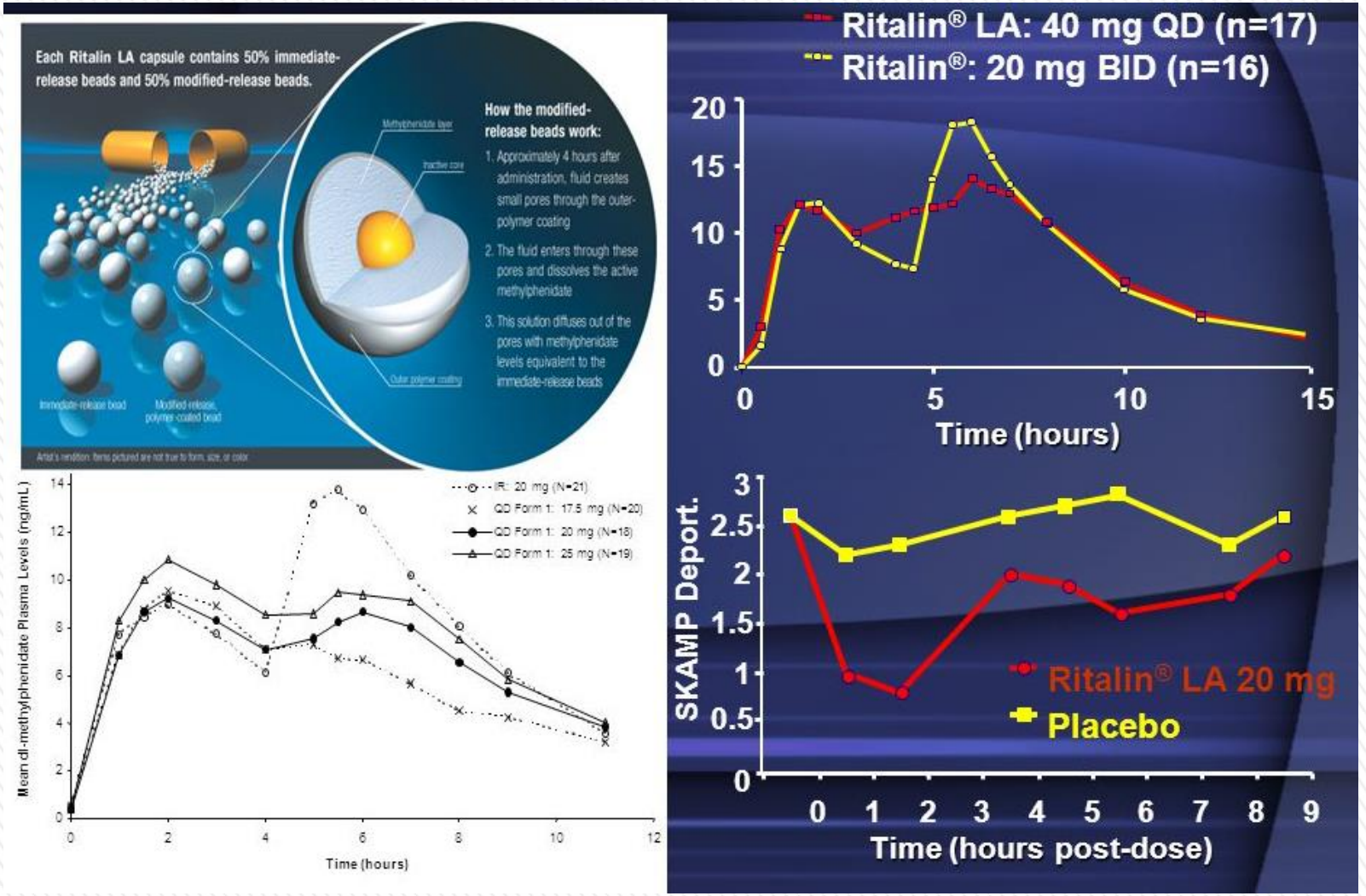
*The highest mean prediction errors is less than 15% for the individual formulations and the highest mean absolute prediction error for the 3 formulations is **6.52%** for Cmax. This value is less than the maximum allowable prediction errors 10% for mean absolute prediction error.*

What is ADHD?

- Psychological disorder characterized by three main traits
  - *Inattention*
  - *Hyperactivity*
  - *Impulsivity*
- These symptoms can make it difficult for a child with ADHD to succeed in school, get along with other children or adults, or finish tasks at home
- ADHD is the most common psychological disorder of childhood, estimated to affect 3% to 9% of school-age children
- 1.29 million children with ADHD are being treated with stimulant medication
- Methylphenidate (MPH) is a stimulant medication used to treat children over 6 years old, adolescents, and adults with attention-deficit hyperactivity disorder (ADHD)

Ritalin LA ® bimodal MPH release for the treatment of ADHD

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



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 (Ritalin1 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.

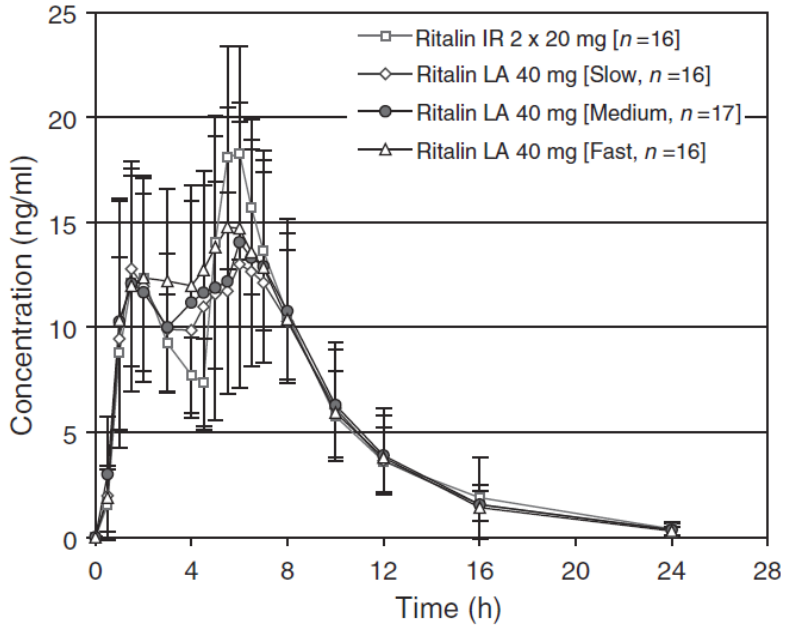


Figure 1. Plasma concentration (mean ± SD)-time profile of MPH after a single dose of Ritalin LA slow-, medium- or fast-release formulation and Ritalin tablets (immediate release formulation) given 4 h apart

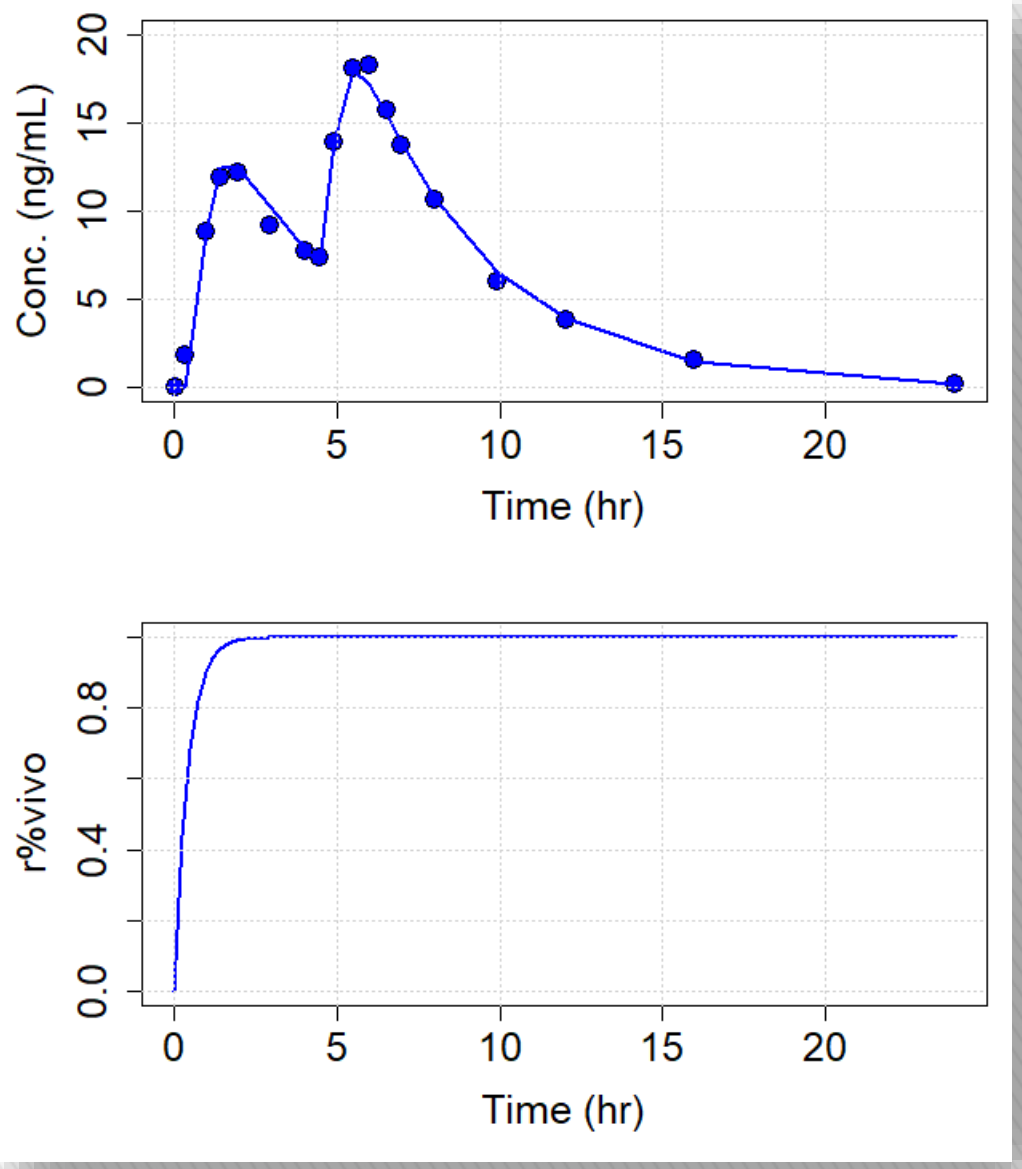
Wang Y, Lee L, Somma R, Thompson G, Bakhtiar R, Lee J, Rekhi GS, Lau H, Sedek G, Hossain M. In vitro dissolution and in vivo oral absorption of methylphenidate from a bimodal release formulation in healthy volunteers. Biopharm Drug Dispos. 2004 Mar;25(2):91-8.

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

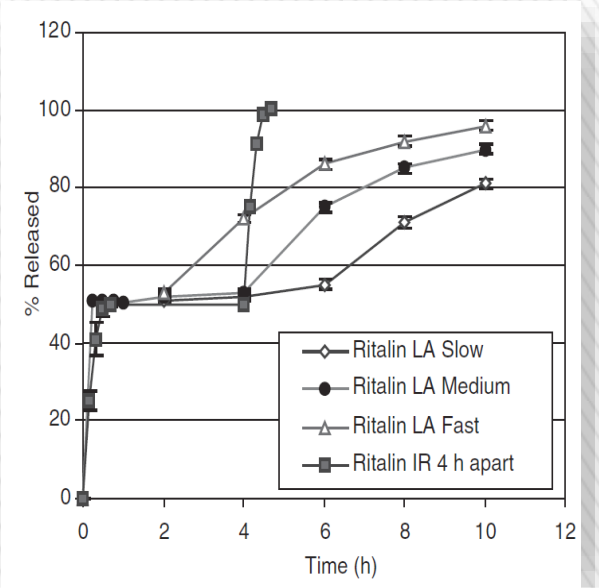
The PK data of Ritalin IR tablets (two 20 mg given four h apart) were considered as the reference and used to estimate the disposition (V) and elimination parameters (kel) of Ritalin

Parameter	Value
ka(hr-1)	2.390
kel(hr-1)	0.254
V(L)	1.200
Lag(hr)	0.633

The value of volume (=**1.20** L) and elimination rate kel (=**0.254** hr-1) were fixed in the assessment of the IVIVC



Step 2: Modelling the in-vitro dissolution data



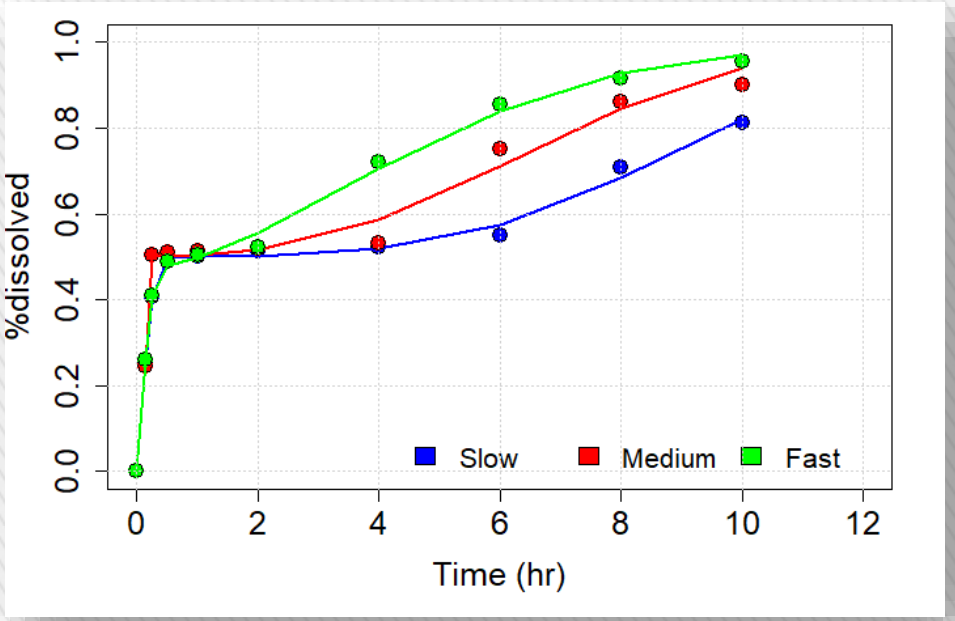
$$\%\text{Dissolved} = \left[1 - \left(\text{ff} \cdot e^{-\left(\left(\frac{\text{time}}{\text{td}}\right)^{\text{ss}}\right)} + (1 - \text{ff}) \cdot e^{-\left(\left(\frac{\text{time}}{\text{td1}}\right)^{\text{ss1}}\right)}\right)\right]$$

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



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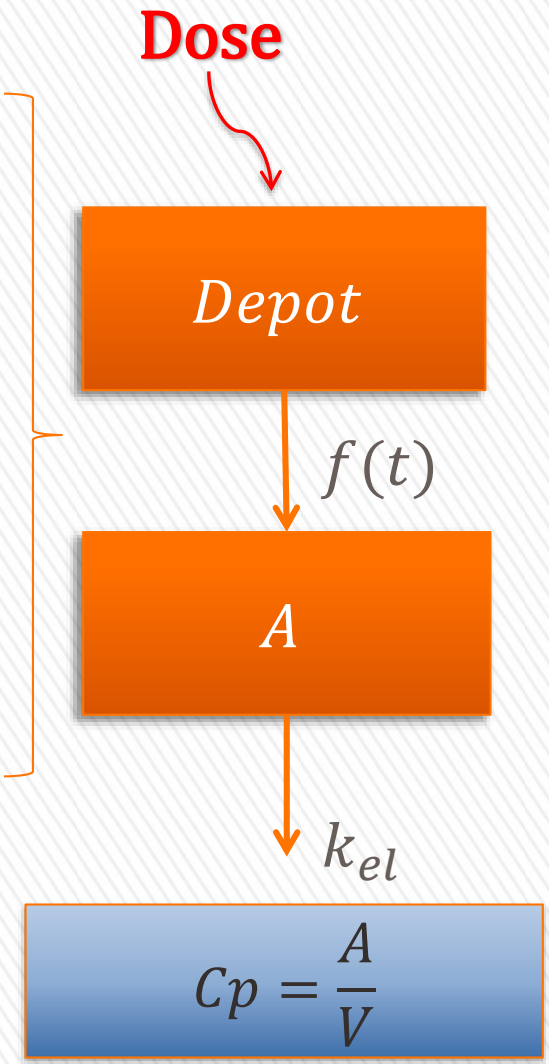
Modeling IVIVC

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

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

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

F_i=*Fraction of the dose available to reach the systemic circulation for the i^{th} formulation*



Implementing IVIVC in NONMEM

```
$PROBLEM  Ritalin IVIVC fit
$INPUT  ID TIME DV DOSE
$DATA  ritapk.csv IGNORE=@
$SUBS  ADVAN13 TOL=8
$MODEL COMP(A)
$PK
IF(ID.EQ.1) THEN
   TD=0.186
   SS=1.7
   TD1=9.91
   SS1=3.59
   FF=0.5
   BI=THETA(6)
ENDIF
IF(ID.EQ.2) THEN
   TD=0.159
   SS=6.55
   TD1=7.55
   SS1=2.63
   FF=0.502
   BI=THETA(7)
ENDIF
IF(ID.EQ.3) THEN
   TD=0.17
   SS=1.79
   TD1=5.42
   SS1=1.75
   FF=0.471
   BI=THETA(8)
ENDIF

  A1=THETA(1)
  A2=THETA(2)
  B1=THETA(3)
  B2=THETA(4)
  B3=THETA(5)
  DELT=0.01
  KEL=0.254*EXP(ETA(1))
  S1=1.2

  ABSO=1-(FF*EXP(-(TIME/TD)**SS)+(1-FF)*EXP(-
(TIME/TD1)**SS1))
  TX=(B1+B2*TIME**B3)
  TX1=(FF*EXP(-(TX/TD)**SS)+(1-FF)*EXP(-(TX/TD1)**SS1))
  VABSO=1-(A1+A2*TX1)
```

```
$DES
  TT1=T-DELT
  TT2=T+DELT
  IF(TT1.LE.0 )TT1=0
  IF(TT2.LE.0)  TT2=0

  TIM=(B1+B2*TT1**B3)
  IF(TIM.LE.0)        TIM=0
  VV=(FF*EXP(-(TIM/TD)**SS)+(1-FF)*EXP(-
(TIM/TD1)**SS1))
  FA=A1+A2*VV
  IF(FA.LE.0) FA=0
  IF(FA.GT.1) FA=1
  ABS1=FA

  TIM=(B1+B2*TT2**B3)
  IF(TIM.LE.0)        TIM=0
  VV=(FF*EXP(-(TIM/TD)**SS)+(1-FF)*EXP(-
(TIM/TD1)**SS1))
  FA=A1+A2*VV
  IF(FA.LE.0) FA=0
  IF(FA.GT.1) FA=1
  ABS2=FA

  KAB=(ABS1-ABS2)/(TT2-TT1)
  DADT(1)=BI*DOSE*KAB-KEL*A(1)
```

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

$$tt = \mathrm{b}_1 + \mathrm{b}_2 \cdot t^{b3}$$

Step 3: Modelling the IVIVC

Two analysis scenarios were considered: in the first one 3 distinct F_ parameters were estimated and in the second one the same F_ value was assumed for the 3 formulations.

Scenario 1: Parameter values estimated assuming a F_ value different for each formulation

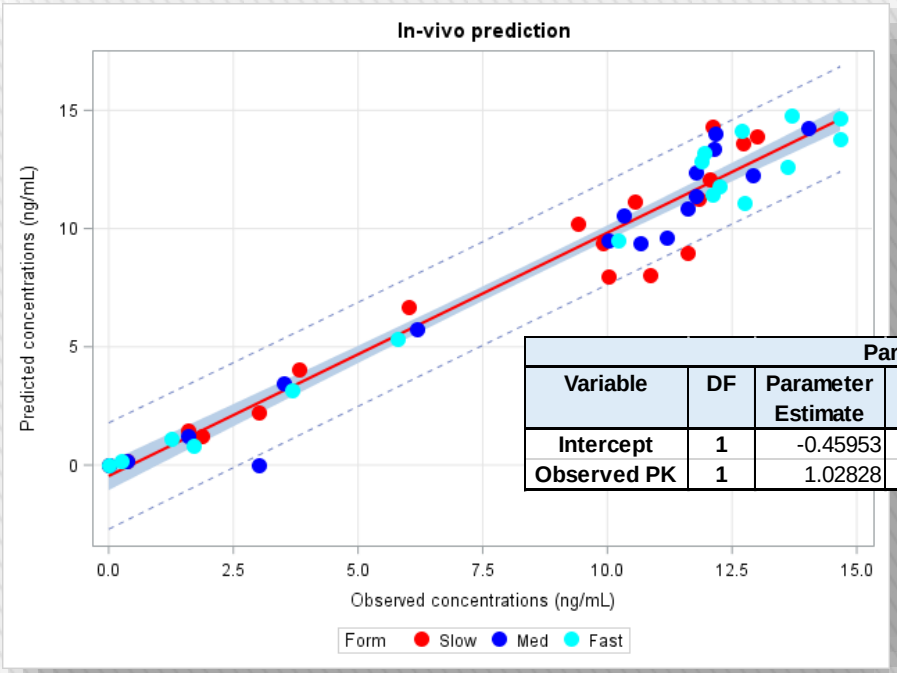
Parameter	Value	FIX	SE	RSE
A1	0	FIX	0	0%
A2	1	FIX	0	0%
B1	0	FIX	0	0%
B2	0.20	-	0.003	1.40%
B3	2.24		0.051	2.30%
F_Slow	0.96	-	0.023	2.40%
F_Medium	0.92	-	0.023	2.50%
F_Fast	0.95	-	0.016	1.70%
err_add	1.12	-	0.096	8.60%
OFV=60.974				

Scenario 2: Parameter values estimated assuming the same F_ value for each formulation

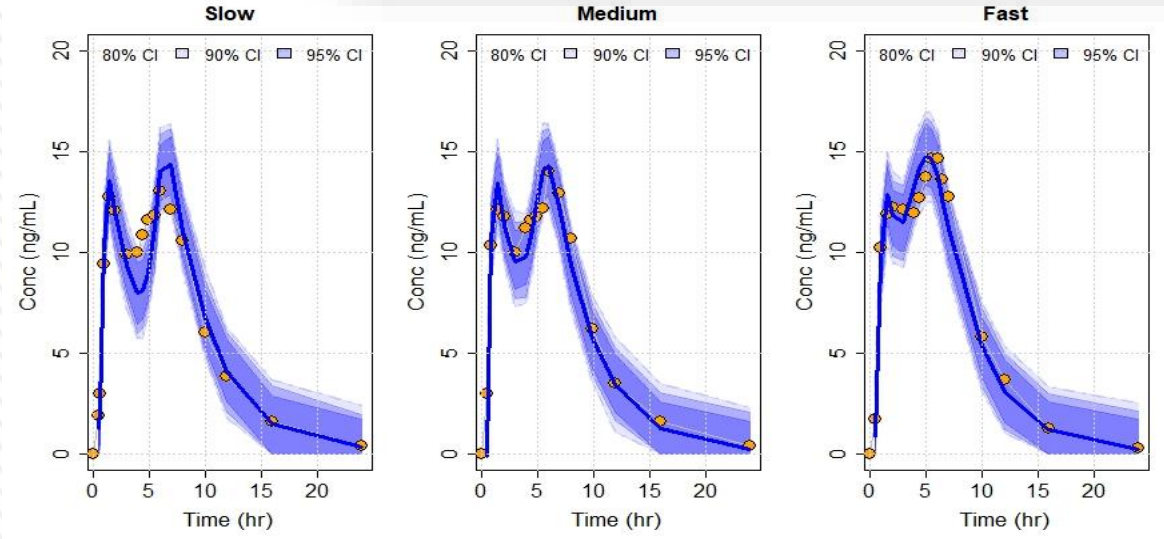
Parameter	Value	FIX	SE	RSE
A1	0	FIX	0	0%
A2	1	FIX	0	0%
B1	0	FIX	0	0%
B2	0.19	-	0.002	1.20%
B3	2.24		0.053	2.40%
F	0.94	-	0.018	1.90%
err_add	1.13	-	0.099	8.80%
OFV=61.402				

OFV is the NONMEM estimated objective function value
The comparison of the change in the OFV value using the log-likelihood ratio test in the two modeling scenarios indicated that the assumption of a common F_ value for the different formulation was the preferred option.

Step 3: 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



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

Additional criteria for assessing predictability (%PE)

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

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

Refined Predictability

0 - 24 hr						
Formulati	cmax_o	auc_o	cmax_p	auc_p	pe_cmax	pe_auc
Slow	13.01	127.46	14.40	127.80	10.68	0.27
Medium	14.02	130.86	14.31	123.38	2.03	5.72
Fast	14.67	133.44	14.69	125.90	0.16	5.65
				Average	**4.29**	**3.88**

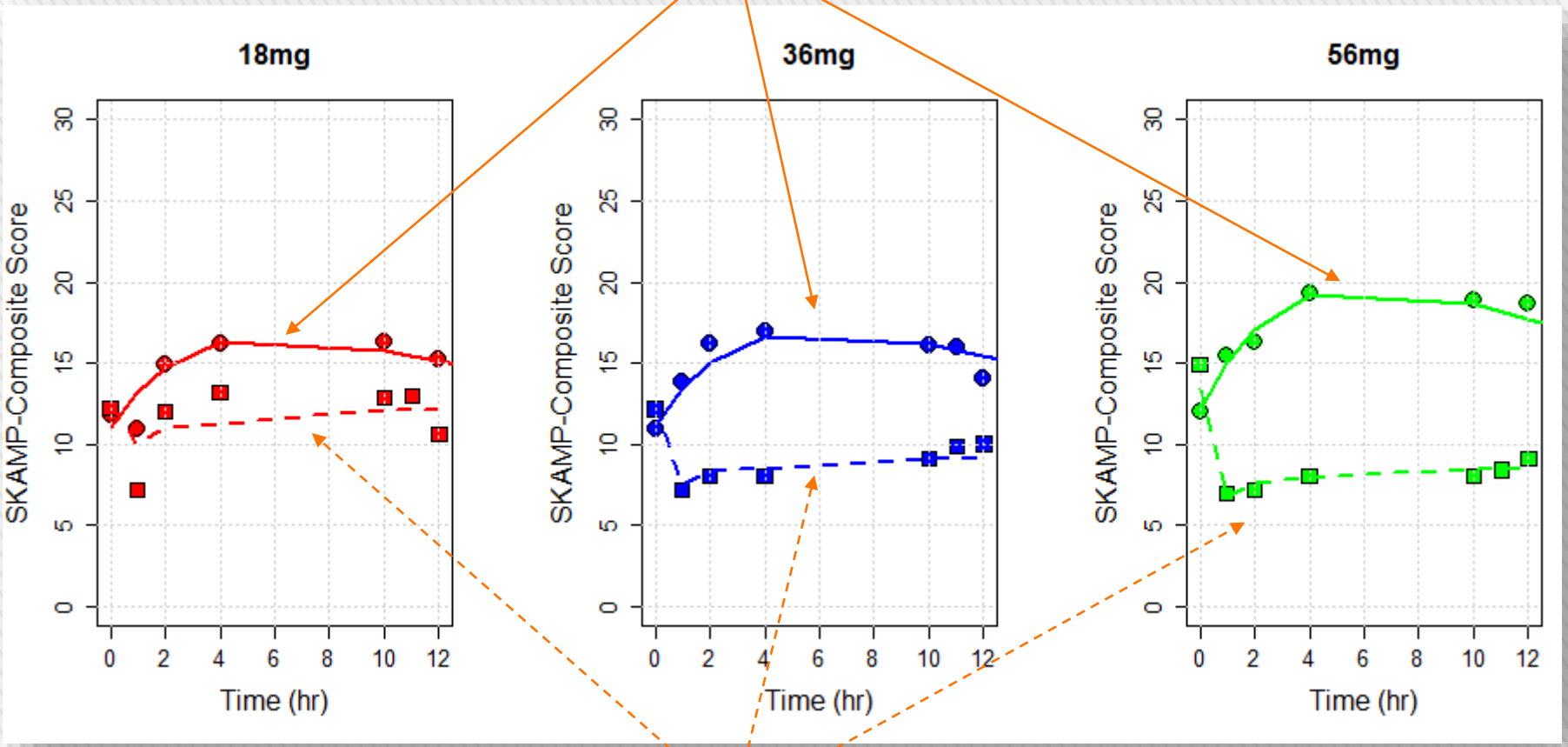
Predictability criteria:

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

0 - 3 hr				3 - 7 hr				7 - 12 hr			
Formulati	auc_o	auc_p	pe_auc	Formulati	auc_o	auc_p	pe_auc	Formulati	auc_o	auc_p	pe_auc
Slow	14.70	15.14	2.95	Slow	44.70	41.84	6.40	Slow	26.25	28.55	8.76
Medium	16.99	16.35	3.77	Medium	46.70	46.32	0.83	Medium	25.96	23.89	7.98
Fast	15.18	14.68	3.30	Fast	45.96	46.83	1.91	Fast	36.63	32.38	11.61
		Average	**3.34**			**Average**	**3.04**			**Average**	**9.45**

The highest mean prediction errors is 11.61% for the individual formulations (<15% max acceptable value) and the highest mean absolute prediction error for the 3 formulations is 9.45 % for pAUC7-12 (<10% max acceptable value)

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



Exposure-response model

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

Where: P(t) is the placebo response defined by the model

$$\frac{dP}{dt} = k_{in} \cdot \left(1 + AA \cdot \left(e^{-t \cdot P1} - e^{-t \cdot P2}\right)\right) - k_{out} P$$

kin = zero-order rate constant for production of response (P),

kout = first-order rate constant for the loss of response;

AA = amplitude of the placebo effect,

P1 and P2 = rate of onset and offset of placebo effect

Delta = score difference at baseline depending on the treatment between assessment days

Emax =maximal MPH related effect

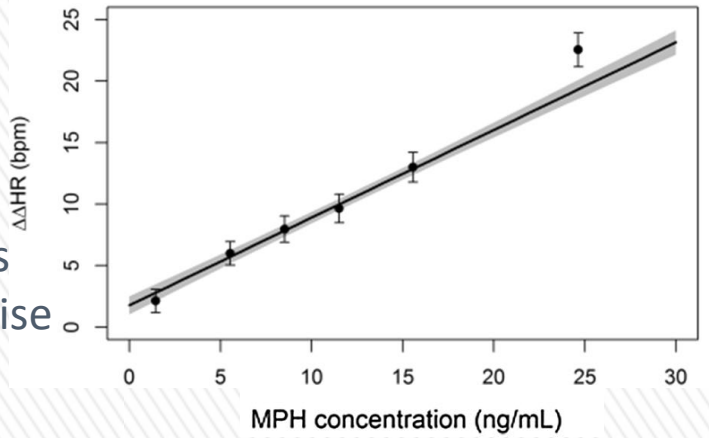
EC_{50} =MPH concentration associated with 50% of the maximal effect

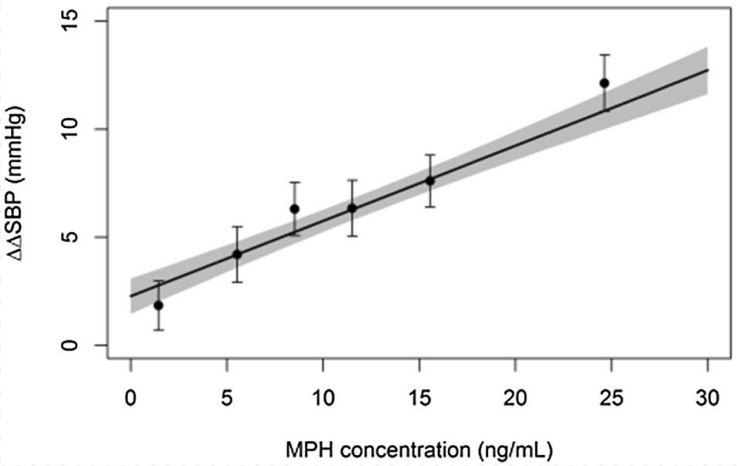
C_p =MPH drug concentration

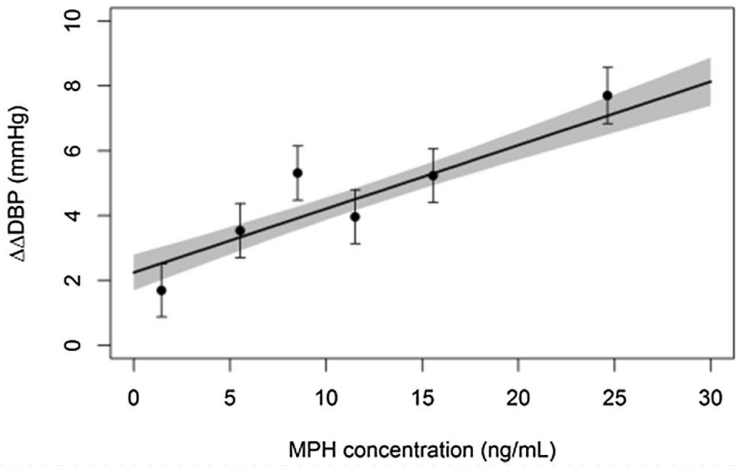
**Gomeni R, Bressolle-Gomeni F, Spencer TJ, Faraone SV, Fang L, Babiskin A. Model-Based Approach for Optimizing Study Design and Clinical Drug Performances of Extended-Release Formulations of Methylphenidate for the Treatment of ADHD. Clin Pharmacol Ther. 2017 Dec;102(6):951-960. doi: 10.1002/cpt.684. Epub 2017 Sep 19.*

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.







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.

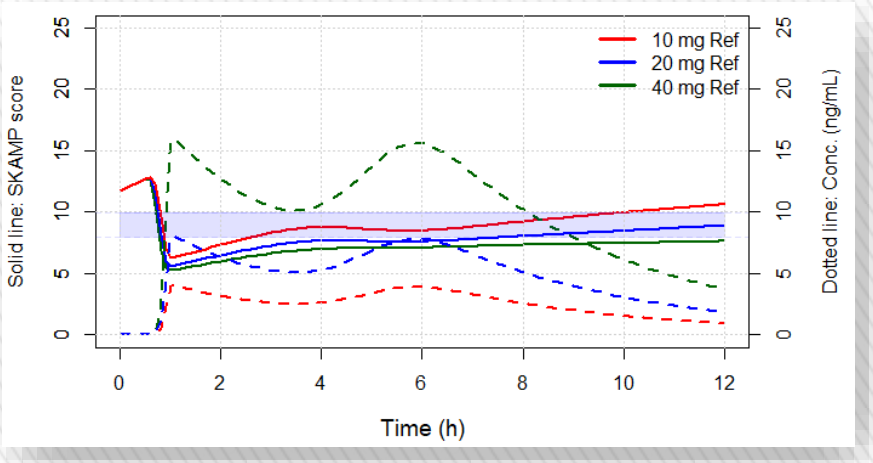
Clinical benefit

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

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

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

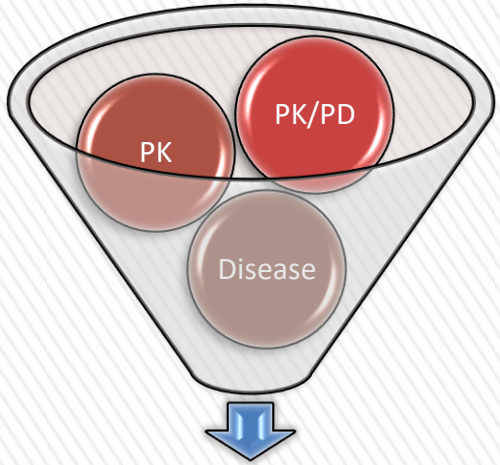
$$\frac{dA}{dt} = F_i * Dose * f(t) - k_{el} \cdot A \Rightarrow Cp = \frac{A}{V}$$



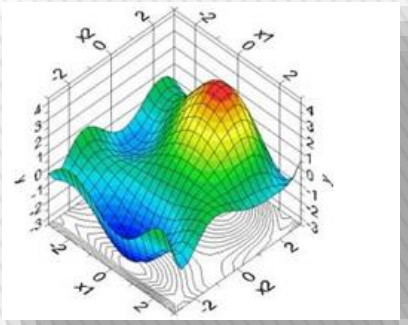
CB=f(SKAMP)

SKAMP=f(Cp)

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

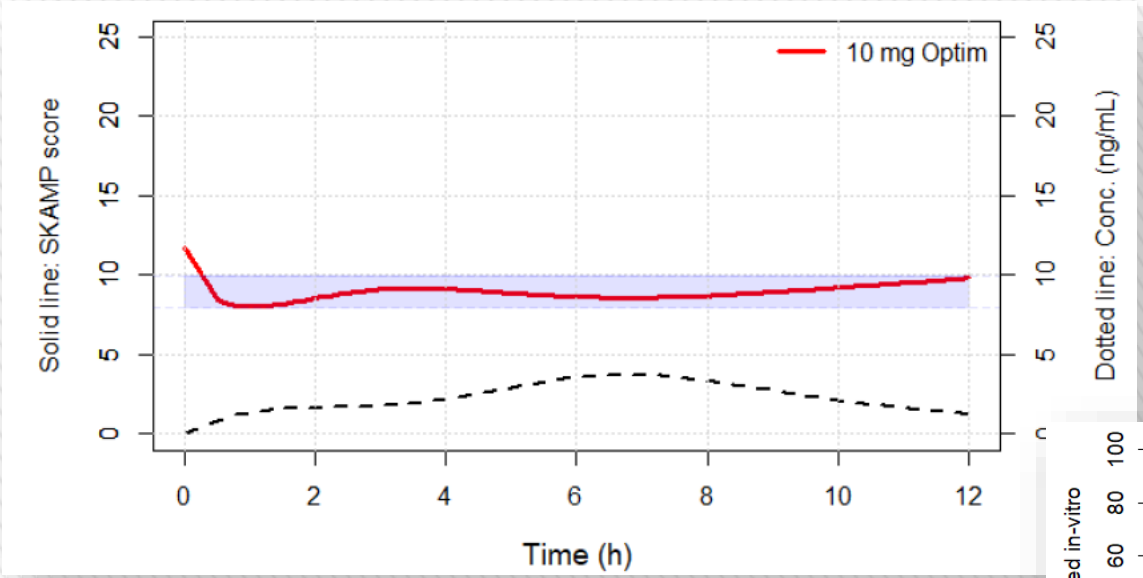


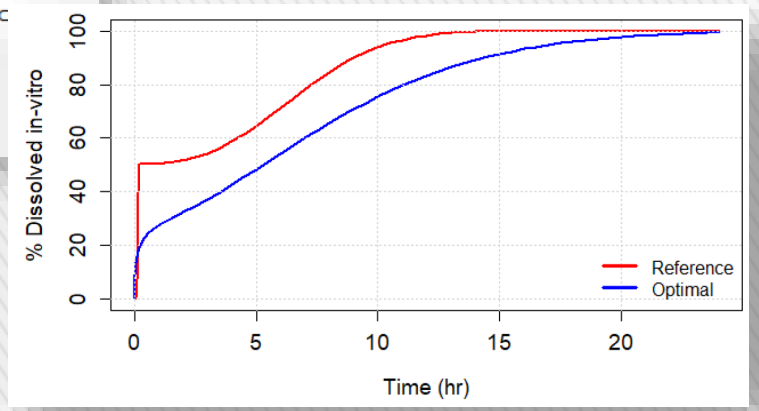
Response variable = Clinical benefit



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

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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