

INTRODUCTION

An *In Vitro – In Vivo* Correlation (IVIVC) is defined by the FDA as “a predictive mathematical model describing the relationship between an *in vitro* property of an extended release dosage form (usually the rate or extent of drug dissolution or release) and a relevant *in vivo* response, e.g., plasma drug concentration or amount of drug absorbed” [1].

These models present the advantage (mainly for modified release formulations) [1] to allow the use of *in vitro* dissolution data early in drug development process, to help **designing/refining formulations**, and as a **surrogate for bioequivalence studies** (scale-up or post-approval changes).

OBJECTIVES

Our aim is to implement an IVIVC model, based on a **population compartmental approach** in order to predict the *in vivo* drug concentration-time profiles with **double-peak absorption** of 3 different modified release (MR) formulations from their respective *in vitro* dissolution fraction-time profiles.

MATERIALS AND METHODS

Data:

- 13 *in vivo* concentration-time profiles per MR formulations from a single 4 period cross-over trial on healthy volunteers after single dose administration of **one immediate release (IR) form** tablet and **one MR form** capsule (slow, intermediate and fast release)
- 6 *in vitro* dissolution fraction-time profiles per MR formulations from *in vitro* capsules dissolution experiment (capsules come from a unique batch for *in vitro* and *in vivo* studies)

Model Building (3 steps):

- In vitro* dissolution fraction-time profile modelling,
- In vivo* IR concentration-time profile modelling,
- In vivo* MR concentration-time profile modelling from *in vitro* and IR results (steps 1 and 2) and from IVIVC model (nonlinear time scaling in order to account for the double peak)

Model Selection and Evaluation Criteria:

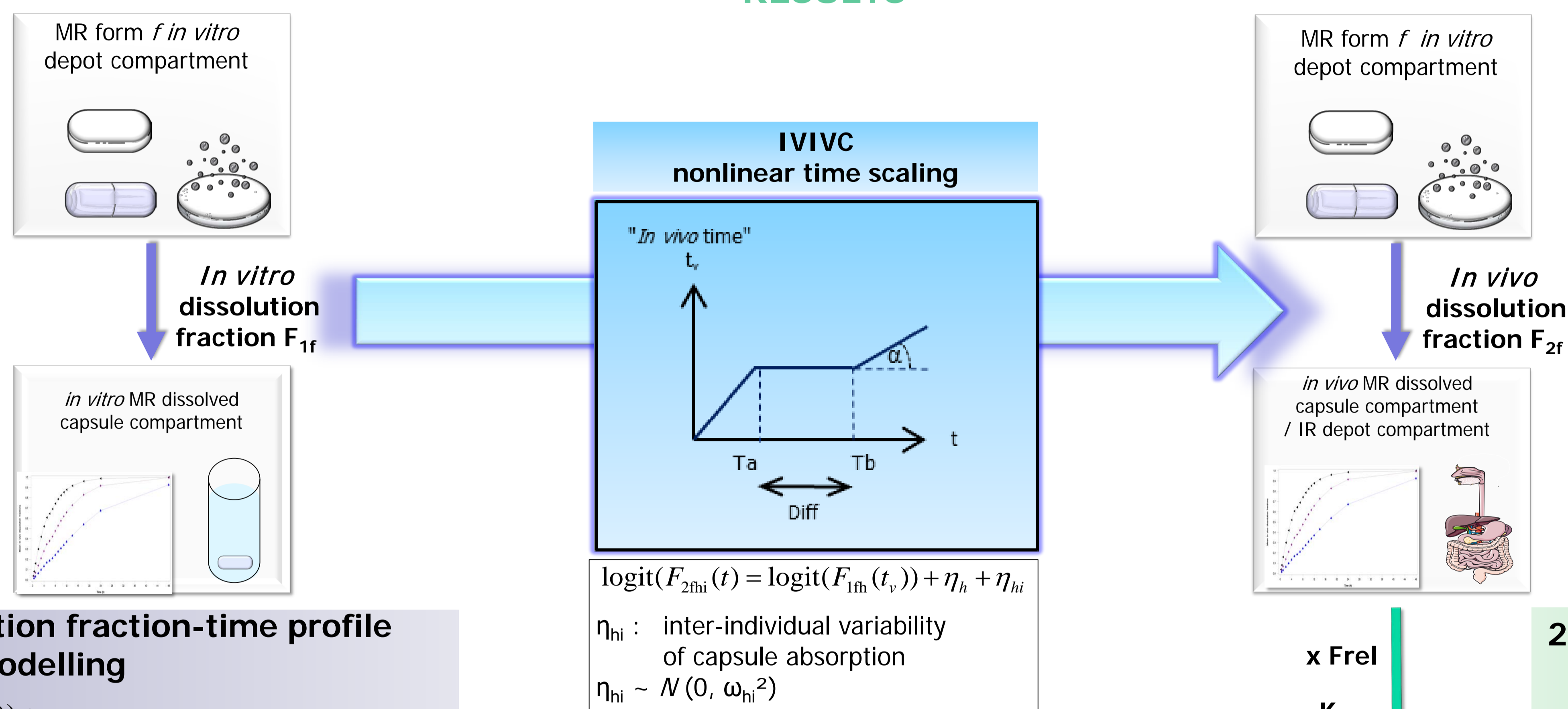
Models were selected by likelihood ratio test ($p=0.05$) using NONMEM objective function. Models that showed good parameter precision of estimation (%RSE < 30% for fixed effects, %RSE < 50% for variances) were then evaluated by visual predictive checks (VPCs), standard goodness-of-fits plots inspection, and individual fits analysis (only VPCs are shown here).

Evaluation of the IVIVC Model:

As recommended in FDA guidance [1], percentage Prediction Error (%PE) on C_{max} and AUC values were used to compare model fits and observations. The guidance recommends %PE should not exceed 15% for any formulation and 10% in average.

$$\%PE_0 = \frac{\theta(\text{obs}) - \theta(\text{pred})}{\theta(\text{obs})} \times 100 \quad \text{where } \theta = \text{AUC or } C_{\text{max}}$$

RESULTS

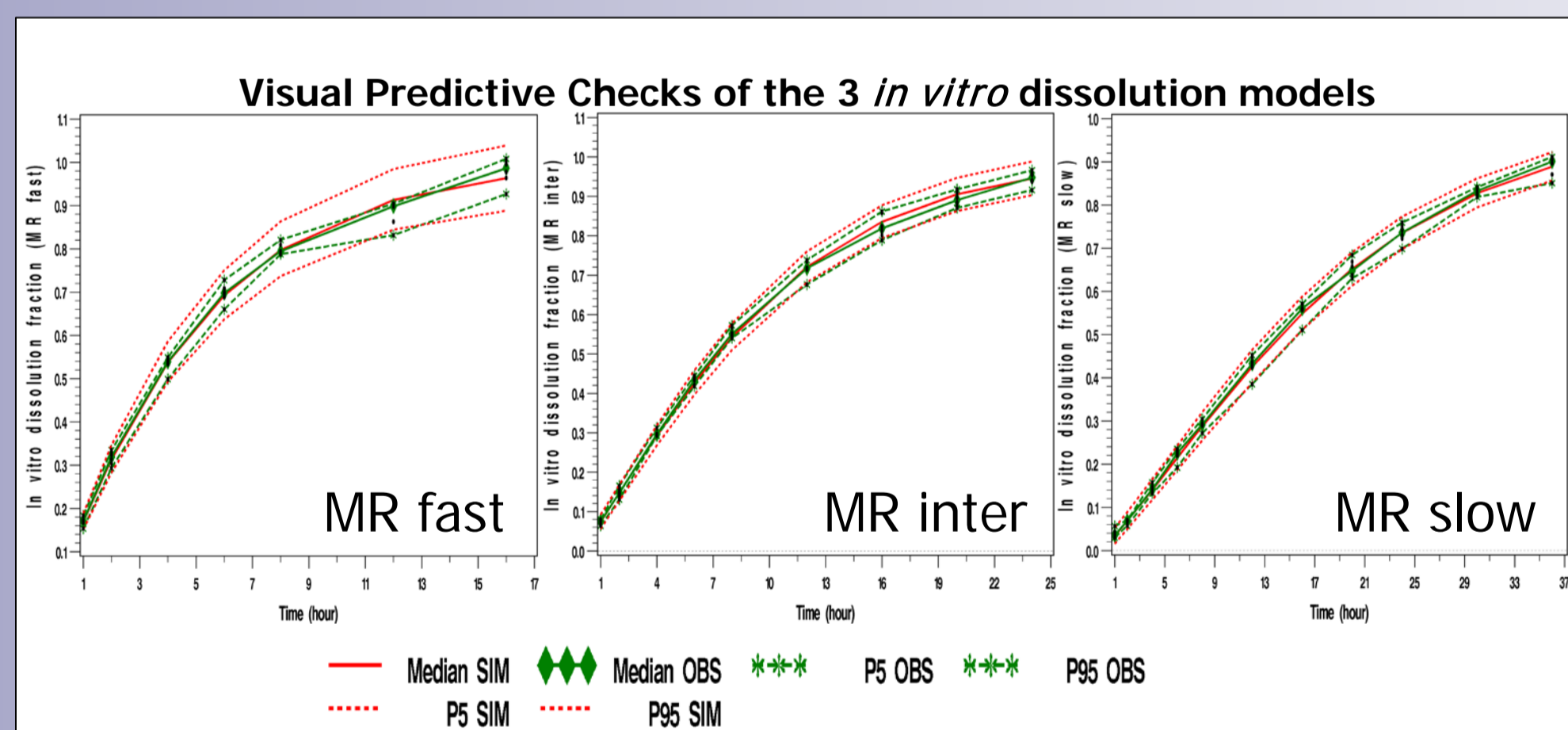


1/ In vitro dissolution fraction-time profile modelling

$$\text{logit}(F_{1h}(t)) = \text{logit}(F_{1f}(t)) + \eta_h$$

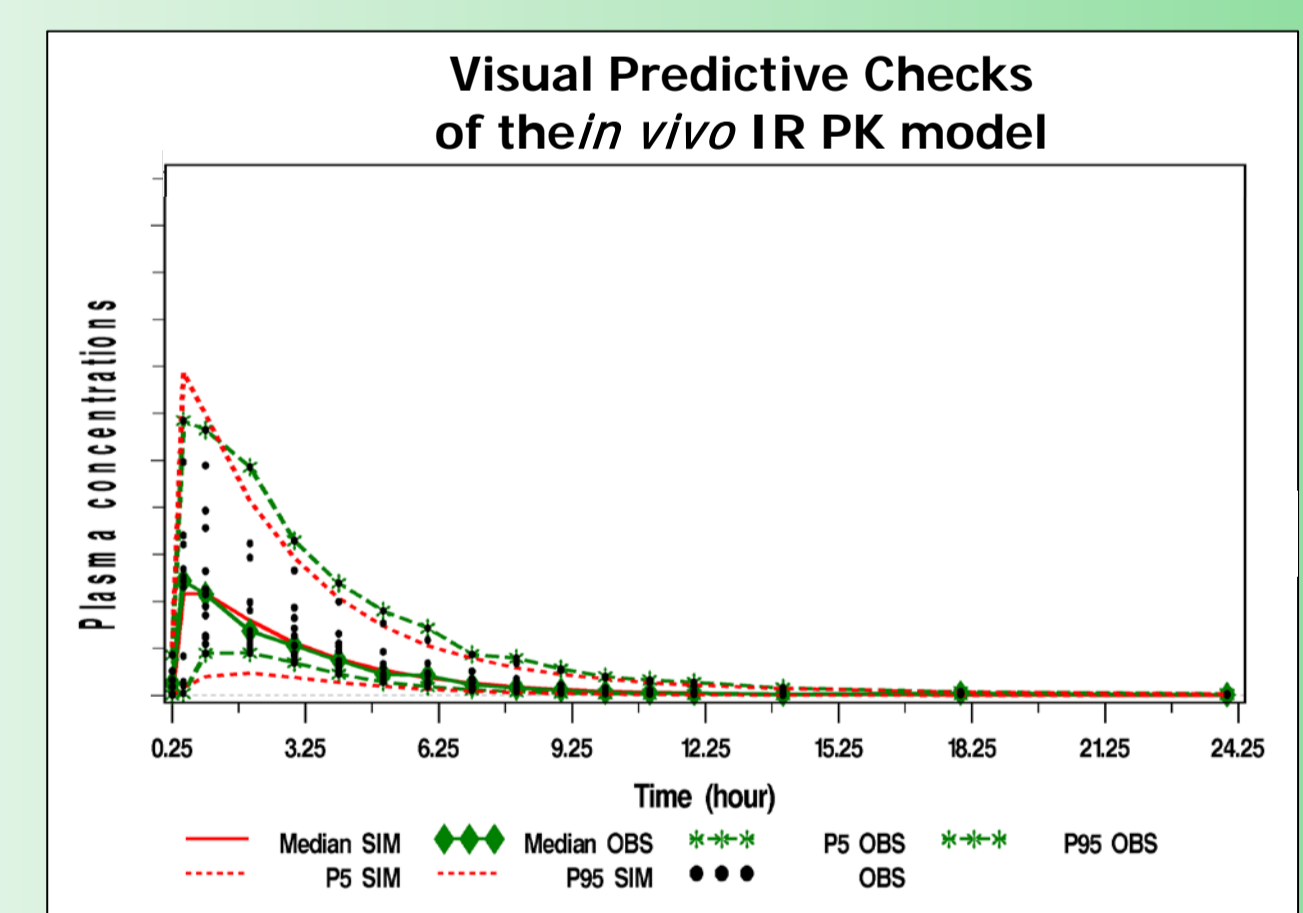
$$F_{1f}(t) = e^{(a_r e^{b_r t})} \quad \text{where } a_r \text{ and } b_r \text{ are specific to MR form } f$$

$\eta_h : \text{inter-capsule dissolution variability}$
 $\eta_h \sim N(0, \omega_h^2)$



2/ In vivo IR concentration-time profile modelling

Concentration time profiles were best described by a 2-compartment model with a first order absorption rate and a lag-time, inter-individual variability on clearance and central volume. The residual error model was proportional.



3/ In vivo MR concentration-time profile modelling from IVIVC model

Model parameter estimates

At this step, the only parameters to be estimated are IVIVC time-scale parameters and variance of relative bioavailability and capsule dissolution in subjects.

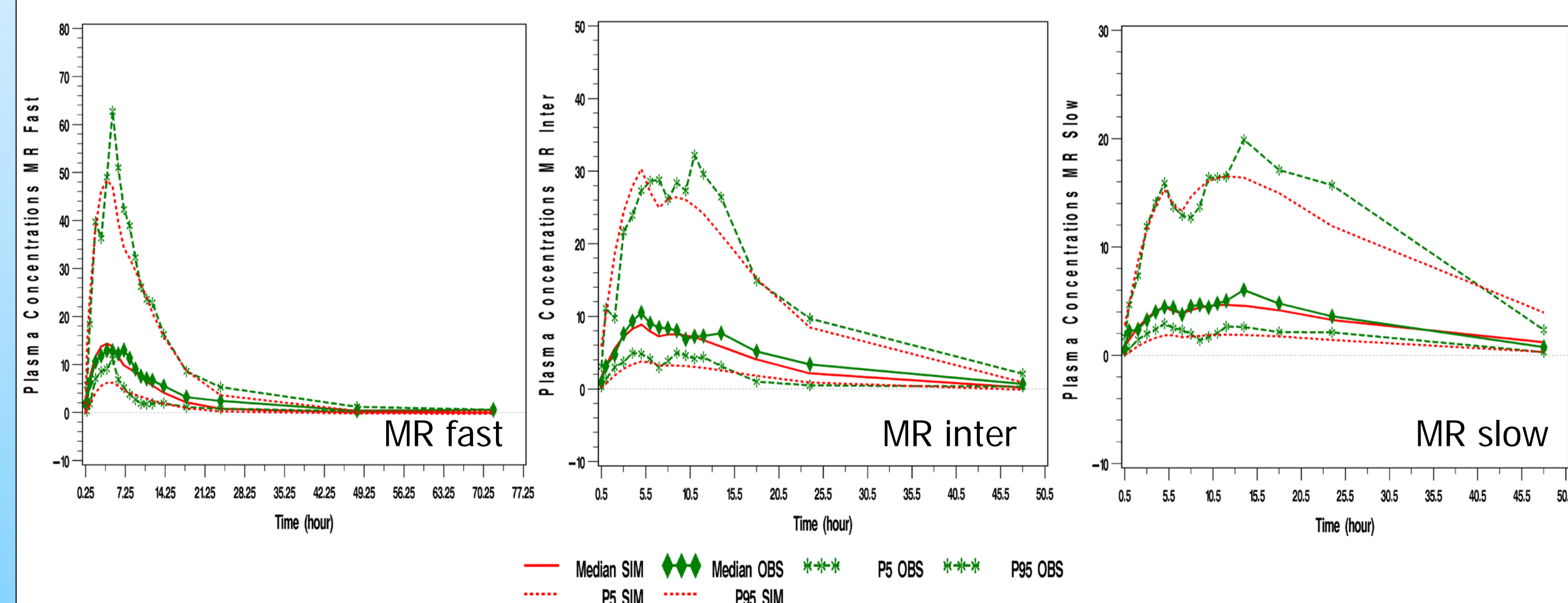
	Ta (h)	Diff (h)	α	Frel	ω_{hi}
Value	5.5	0.76	0.91	1 (fixed)	-
IIV (%)	-	-	21	27	12

Combined residual error model:

$$\sigma_{\text{prop}} = 20.1\%$$

$$\sigma_{\text{add}} = 0.964$$

Visual Predictive Checks of the 3 in vivo MR from IVIVC model



Computation of %PE with AUC and C_{max}

	MR Fast	MR Inter	MR Slow	Mean
%PE _{C_{max}}	4%	2%	14%	6.7%
%PE _{AUC}	16%	9%	2%	9%

CONCLUSION

This work illustrates another application of a population PK approach [2] to IVIVC model building, adding an **accurate individual description of complex absorption** concentration-time profiles, exhibiting a double peak, which would not be possible with a classical IVIVC method. The model could be improved, especially regarding highest concentration values (second peak of 95th percentile). This is valuable for evaluation of further formulation in development, **not limited to a mean profile adequate fitting**. Percentage prediction error are also very close to be satisfactory compared to guideline requirements.

REFERENCES

[1] Food and Drug Administration (1997) Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of *In Vitro/In Vivo* Correlations.

[2] Clare Gaynor, Marylène Gagnet, Marylore Chenel, Developing an In Vitro – In Vivo Correlation Model Using a Population Approach in NONMEM, PAGE 20 (2011) Abstr 2099 [www.page-meeting.org/?abstract=2099]