Physiologically Based Pharmacokinetic Modeling and Mechanistic *In Vitro-In Vivo* Correlation for Long-Acting Injectable Suspension

Daniela Amaral Silva[1], Viera Lukacova[1], Khondoker Alam[2], Eleftheria Tsakalozou[2], Abdullah Al Shoyaib[2]
[1]Simulations Plus, Inc, USA.; [2]Food and Drug Administration (FDA), USA

Introduction

Long acting injectable (LAI) suspensions demonstrate extended release by forming depots at the injection site (subcutaneous or intramuscular), from which poorly soluble drugs are slowly dissolved and absorbed into the systemic circulation. Developing complex generic LAIs is often challenging. Establishing mechanistic in vitro–in vivo correlations (IVIVC) based on physiologically based pharmacokinetic (PBPK) models is a valuable approach for advancing LAI drug product development. This study aimed to establish an IVIVC approach paliperidone palmitate once-monthly extended-release LAI suspension formulations in rat and human.

Methods

PBPK modeling was performed using GastroPlus® 9.9. A compartmental PK model was built for rat based on intravenous (IV) and intramuscular (IM) solution data (1). A perfusion-limited human PBPK model was built using the Lukacova method to calculate the plasma partition coefficients (2-3). Physicochemical properties were obtained from the literature (4) or predicted from the drug chemical structure using ADMET Predictor® (Version 11). Mechanistic deconvolution was performed to obtain the predicted in vivo dissolution profiles in rat and human (4-5). An in vitro in vivo relationship (IVIVR) was established in rats and used to inform a level A mechanistic IVIVC in humans. Human IVIVC was established with three formulations and one additional formulation for external validation.

Results

The developed PK models for paliperidone adequately described the plasma concentration (Cp) profiles following IV infusion and oral solution in human (R2 = 0.74 and 0.87, respectively) and IV (R2 = 0.99) and IM solution in rat.

The established models were used to deconvolute the Cp-time profiles after IM administration of paliperidone palmitate once-monthly LAI suspension in rat and human. Preclinical and clinical IVIVCs were established between the in vivo and in vitro dissolution profiles, according to equations 1 and 2, respectively.

$$\ln(t^*) = 5.90 + 0.37\ln(t) + 0.002\ln(t)^2 + 0.87\,Fr_Q \quad \text{Equation 1}$$

$$\ln(t^*) = 5.91 + 0.17\ln(t) - 0.016\ln(t)^2 + 2.59\,Fr_Q \quad \text{Equation 2}$$

In which t* is the scaled in vitro time and Fr_Q is the fraction in vitro release.

This IVIVC using the time scaling approach resulted in an overall successful prediction of plasma concentrations for both species (Table 1, Figures 1-2). The Cmax and AUC prediction errors (PEs) were 14.6% and 0.6%, respectively in the case of the rat model. The Cmax and AUC PEs were between 4.4% and 10%, for internal validation and 12.8% for both Cmax and AUC for the external validation.

Results

Table 1. Comparison of Cmax and AUC prediction errors after IM administration of paliperidone palmitate once-monthly LAI suspension in rat and human

Rat	**Marketed formulation**		
			%PE
Cmax (ng/mL)	78.06	66.62	-14.65
AUC 0-t (ng-h/mL)	27620	27460	-0.58
Human		**Slow**	
			%PE
Cmax (ng/mL)	5.97	6.24	4.40
AUC 0-t (ng-h/mL)	8677.1	8338.5	-3.90
Human		**Intermediate**	
			%PE
Cmax (ng/mL)	7.63	7.91	3.66
AUC 0-t (ng-h/mL)	8584.7	9439.5	9.96
Human		**Fast**	
			%PE
Cmax (ng/mL)	8.70	8.50	-2.33
AUC 0-t (ng-h/mL)	10370	9770.7	-5.78
Human Average Absolute PE Cmax			3.46
Human Average Absolute PE AUC			6.55
Human		**External Validation**	
			%PE
Cmax (ng/mL)	7.27	8.20	12.82
AUC 0-t (ng-h/mL)	8354.8	9425.9	12.82

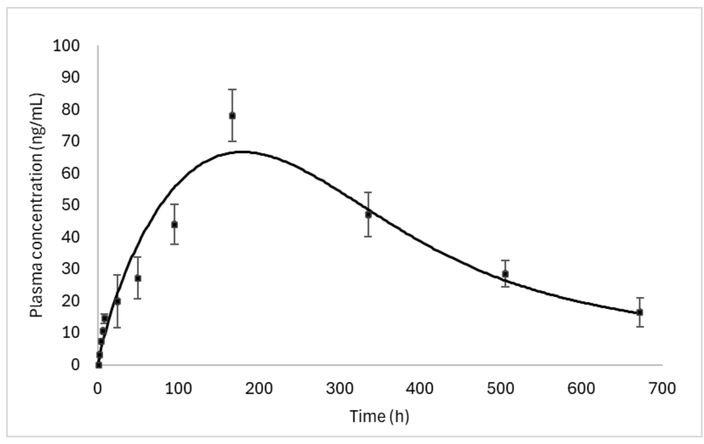

Figure 1. Observed (squares) and predicted (line) plasma concentration vs time profile after IM administration of paliperidone palmitate once-monthly LAI suspension in rat. Prediction based on mechanistic IVIVR using time scaling approach.

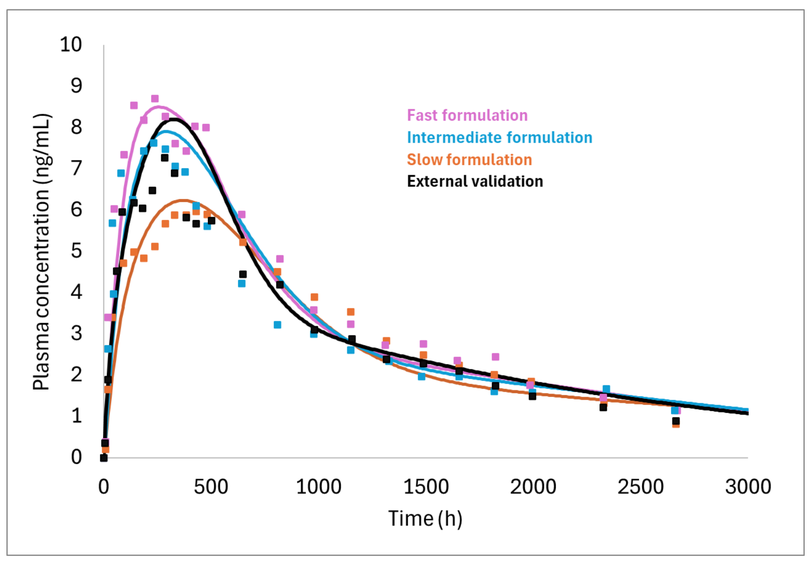

Figure 2. Observed (squares) and predicted (line) plasma concentration vs time profile after IM administration of paliperidone palmitate once-monthly LAI suspension in humans. Prediction based on mechanistic IVIVC using time scaling approach.

Conclusion

The preclinical IVIVR and clinical mechanistic IVIVC approach resulted in reasonable predictions of the systemic exposure of paliperidone palmitate once-monthly LAI suspension both in rat and human. Establishing IVIVC for LAIs is challenging given the need for time scaling, hence further studies are needed to refine this strategy. Preclinical data can be useful in establishing the IVIVC approach towards clinical predictions.

References

(1)Darville N., et al. J Contr Rel. 2016:95-108
(2)Samtani M.N., Vermeulen A., Stuyckens K. Clin Pharmacokinet. 2009:585–600
(3)Vermeir M., et al. Drug Metab and Disp. 2008:769-779
(4)New Drug Application 22264. 02/03/2009 – Invega SustennaTM
(5)Li J., et al. EJPB. 2025 :114613.

Acknowledgements

This research was funded through the FDA Office of Generic Drugs; Contract # 75F40121C00133. The views expressed here do not reflect official policies of the US FDA or the Department of Health and Human Services, nor does any mention of trade names imply endorsement by the US Government.

SimulationsPlus