U.S. FOOD & DRUG ADMINISTRATION

PBPK Modeling to Support the Expansion of Biowaiver to Non-Q1/Q2 BCS Class III Drug Products

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INTRODUCTION

Current ICH M9 guidance[1] suggests that a waiver request of in vivo bioequivalence (BE) studies for a BCS Class III product may be considered if it demonstrates high solubility, very rapid dissolution (≥85% dissolved in ≤15 minutes for both test product and reference listed drug (RLD), and the test product formulation is qualitatively (Q1) same and quantitatively (Q2) similar to the RLD. The purpose of this research is to use PBPK modeling to determine dissolution safe space to support possible expansion of biowaiver to non-Q1/Q2 BCS Class III drug products using nadolol immediate release (IR) tablets as an example.

METHOD

PBPK model using GastroPlus™ 9.9 (Simulations Plus Inc., CA, USA) was developed in house for nadolol IR tablets. Physicochemical properties, in vitro dissolution data, pharmacokinetic (PK) data and parameters obtained from the literature[2-6] and regulatory submissions (in-house data) were used as model input to develop and validate the PBPK model for nadolol IR tablets under fasted conditions. In this model, the dissolution data were incorporated using Z-factor dissolution model. Parameter sensitivity analysis (PSA) were conducted to evaluate the impact of effective permeability (P_{eff}) and Z-factor on BE parameters (C_{max} and AUCs). For the model application, virtual BE (VBE) simulations were conducted to evaluate the impact of non-comparable in vitro dissolution on the predicted systemic exposure, and overall BE determination for the generic nadolol IR tablets and RLD. Additional VBE simulations were conducted by incorporating different theoretical dissolution profiles with different release rates (i.e., different Z-factor values) to determine dissolution safe space. Figure-1 shows the general workflow for development, validation, and application of the PBPK model for nadolol IR Tablets.

RESULTS

Development and validation of nadolol oral PBPK model under fasted conditions accurately predicted (prediction errors <20%) PK profiles of different strengths (1, 2, 10, 30, 60 and 80 mg). PSA showed that BE parameters (C_{max} and AUCs) are sensitive to P_{eff} values and Z-factor values.

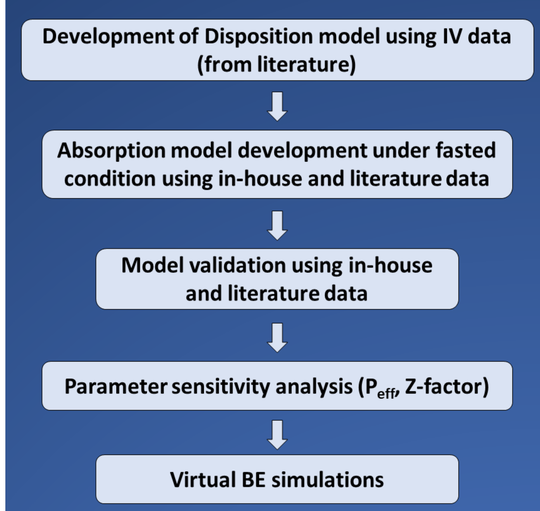

Figure-1: General workflow for development, validation, and application of the PBPK model for nadolol IR tablets.

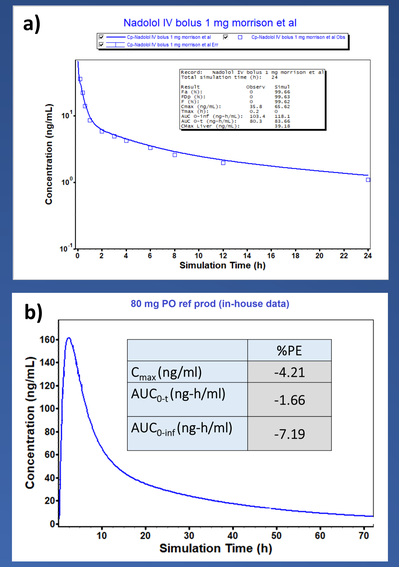

Figure-2: a) Disposition model development for nadolol IR tablets using IV data from literature; b) absorption model development for nadolol IR tablets using in-house data under fasted condition.

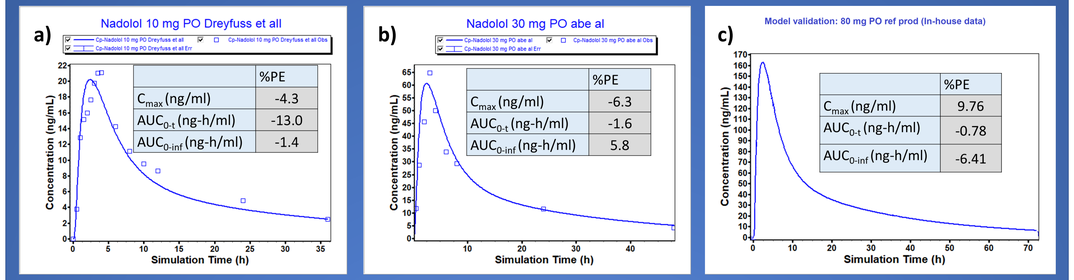

Figure-3: Validation of the PBPK model for nadolol IR tablets using literature (a and b) and in-house (c) data.

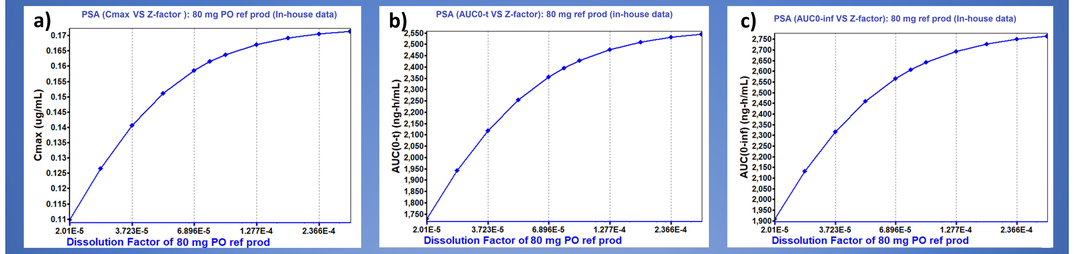

Figure-4: Parameter sensitivity analysis (PSA) of BE parameters, C_{max} (a), AUC_{0-t} (b) and AUC_{0-inf} (c) against Z-factor values (using in-house data). [Note: A similar finding was obtained from the PSA of P_{eff} values (results not shown here)].

RESULTS (Cont.)

VBE simulations showed that PBPK model prediction by incorporating experimental non-similar dissolution profiles (F2<50) did not result in significant difference in drug exposure, indicating a low risk of non-BE between generic and RLD. In addition, dissolution safe spaces were determined based on further VBE simulations by incorporating different theoretical dissolution profiles with different release rates.

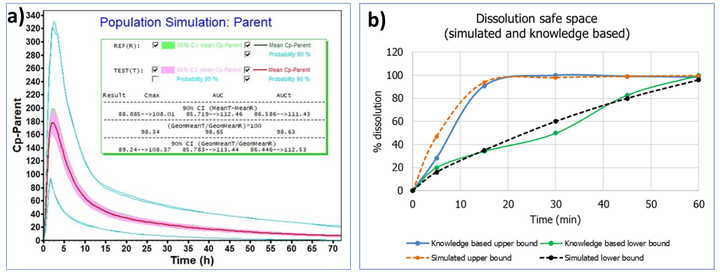

Figure-5: **a)** Representative VBE simulations under fasted conditions showing BE between generic test product and RLD using non-similar dissolution profiles (i.e., F2<50); **b)** Simulated and knowledge-based dissolution safe spaces under fasted conditions. Dissolution safe spaces were determined from additional VBE simulations using theoretical dissolution profiles with different release rates (i.e., different Z-factor values).

CONCLUSION

PBPK modeling and VBE simulations demonstrated that non-Q1/Q2 nadolol IR tablets with dissimilar dissolution profiles are of low risk for non-BE, when the dissolution profiles are within the suggested dissolution safe space. The presented PBPK modeling approach may be utilized to identify a dissolution safe space and expand biowaiver to other non-Q1/Q2 BCS Class III drug products.

Disclaimer: This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

References:

1. ICH M9 Guidance: https://www.fda.gov/media/148472/download
2. Morrison et al, Eur J Clin Pharmacot (1988) 33:625-628
3. Dreyfuss et al. J Clin Pharmacol (1977) May-Jun;17(5-6):300-7
4. Dreyfuss et al. J Clin Pharmacol (1979) Nov-Dec;19(11-12):712-20
5. Abe et al. European Journal of Clinical Pharmacology (2018) 74:775–783
6. Schäfer-Korting et al. Eur J Clin Pharmacol (1984) 26:125-127