# Comparison of Common Methodologies for Accounting for IIV for Oral Bioavailability in the Absence of Intravenous Data

Anne Brochot[1], Soha Freidy[2], Kai Bartlette[2], Alex MacDonald[3]

1 Allucent BVBA, Testelt, Belgium; 2 Allucent LLC, Cary, NC, USA; 3 Allucent Limited, Bracknell, UK.

## Introduction

The oral bioavailability (F) of a drug is the product of the fraction absorbed (Fa), the fraction escaping the gut-wall metabolism (Fg), and the fraction escaping liver extraction (Fh). Every component of this product can be influenced by several factors such as the physicochemical properties of the drug or physiological issues (1). In turn, each of those factors contributes to potential inter-individual variability (IIV) in bioavailability. When modeling oral pharmacokinetic (PK) data using a nonlinear mixed effect method, two approaches are commonly used in the absence of intravenous (IV) data:

1. Attribute the IIV linked to F to the apparent clearance (CL/F) and the apparent volume of distribution (V/F) parameters and estimate the potential correlation between the two;
2. Fix the bioavailability to a relative value of 1 and estimate an IIV on this parameter.

While the modeling of oral or other extravascular PK data in the absence of corresponding intravenous data is common practice in drug development, there appears to be no clear consensus in the literature as to the most appropriate methodologies or a comparison of their relative merits. The objective of this analysis was to evaluate the suitability of these approaches.

## Methods

A simulation-re-estimation approach was undertaken to compare the 2 modeling methods. Creating virtual models within NONMEM® was initially considered for the simulations. However, to make the exercise representative of real-life data and plausible molecule physicochemical and physiological properties, physiologically-based pharmacokinetic (PBPK) models of drugs from publicly available libraries in PK-Sim® (2) were used to simulate clinical study data with a phase 1 single ascending dose-like design with a dense sampling strategy. Six drugs of different BCS class (verapamil and fluconazole, BCS class 1; montelukast and felodipine, BCS class 2; dapagliflozin and cimetidine, BCS class 3) were simulated. The doses, sampling times, and drug formulations were selected based on PK-Sim® reports available for each drug (only immediate-release tablets or solutions formulations from PK-Sim® libraries were used). The PK-Sim® bioavailability was output for each simulated subject in addition to concentration-time data and virtual subjects' demographics. The following table shows the virtual study design for each drug:

| Drug | BCS Class | Doses | Sampling Times |
|---|---|---|---|
| Verapamil | 1 | 40, 80, 120, 240, 400, 480 mg | Predose, 5, 10, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 24 h post-dose |
| Fluconazole | 1 | 50, 100, 150, 200, 400, 800 mg | Predose, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96 h post-dose |
| Montelukast | 2 | 2, 4, 5, 10, 18, 50 mg | Predose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36 h post-dose |
| Felodipine | 2 | 1, 5, 10, 20, 40 mg | Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24 h post-dose |
| Dapagliflozin | 3 | 2.5, 5, 10, 20, 50, 100, 250, 500 mg | Predose, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 18, 22, 24 h post-dose |
| Cimetidine | 3 | 100, 200, 300, 400, 800 mg | Predose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 9, 10, 12 h post-dose |

Data programming to transform the simulation files from PK-Sim® to NONMEM readable datasets was performed in R v4.1.3 (http://www.r-project.org), with a single dataset for each drug. The data were then modeled using NONMEM V7.4 (ICON Development Solutions, Ellicott City, MD) and Pirana version 2.9.8 (Certara, Princeton, NJ). Graphical evaluations were performed using R. Bodyweight allometric scaling was introduced apriori on all apparent clearance and volume terms. Model evaluation was based on goodness-of-fit plots, prediction-corrected visual predictive checks (pcVPC), and precision in parameter estimates. The best model without an IIV on F was determined for each drug and then IIV on F was included. The relationship between the post-hoc Eta for F and the PK-Sim® bioavailability was evaluated.

## Results

All models included an IIV on CL/F and V/F as a minimum, except for fluconazole (IIV on absorption rate parameter only) and montelukast (IIV on CL/F and peripheral distribution parameters). Partial or full correlation blocks were introduced where required. All models showed good predictive performance based on the pcVPC, excluding fluconazole for which a dose dependency on absorption parameter was suspected as classical VPC appeared appropriate. Except for verapamil, all models showed a decrease in both objective function value (OFV), Akaike information criteria (AIC), and residual unexplained variability (RUV) when an IIV on F was introduced. This improvement did not translate into significant enhancement of the pcVPCs, but a correlation between the post-hoc Eta for F and the PK-Sim® derived bioavailability was observed in most cases.

## Conclusion

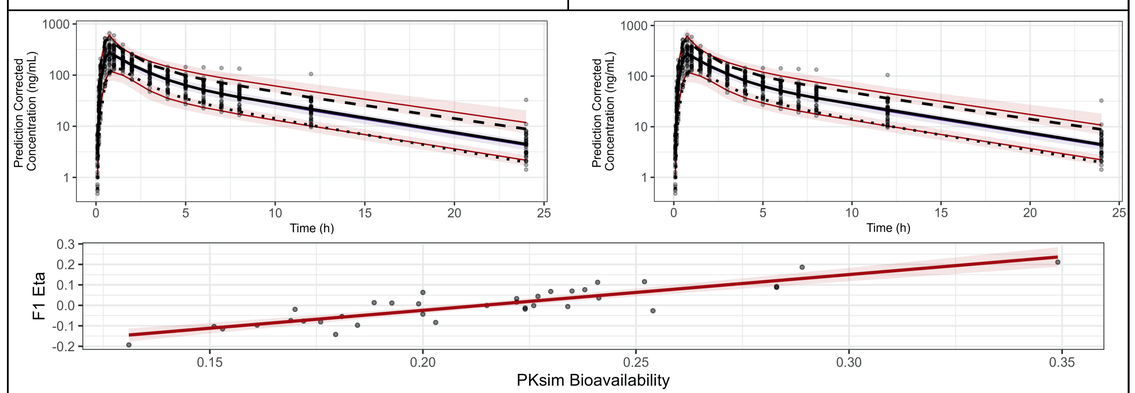
NONMEM was able to quantify the IIV on F in addition to apparent CL and V terms, its presence improved the OFV and RUV in most cases, and was generally correlated to the "true" bioavailability. Importantly, the choice to use an IIV on F, while not necessarily improving the predictive performances, could be made based on the objective of the modeling exercise, e.g. some F-specific covariates are suspected or if RUV is important for future simulations.

1. Rowland and Tozer's Clinical Pharmacokinetics and Pharmacodynamics. Concept and applications. H. Derendorf, S. chmidt. Fifth edition. Wolters Kluwer, 2020.
2. https://www.open-systems-pharmacology.org/

**Verapamil**

Parallel ZO-FO absorption, 1 cmt, IIV on CL/F and V/F, no block. OFV=-1125.304

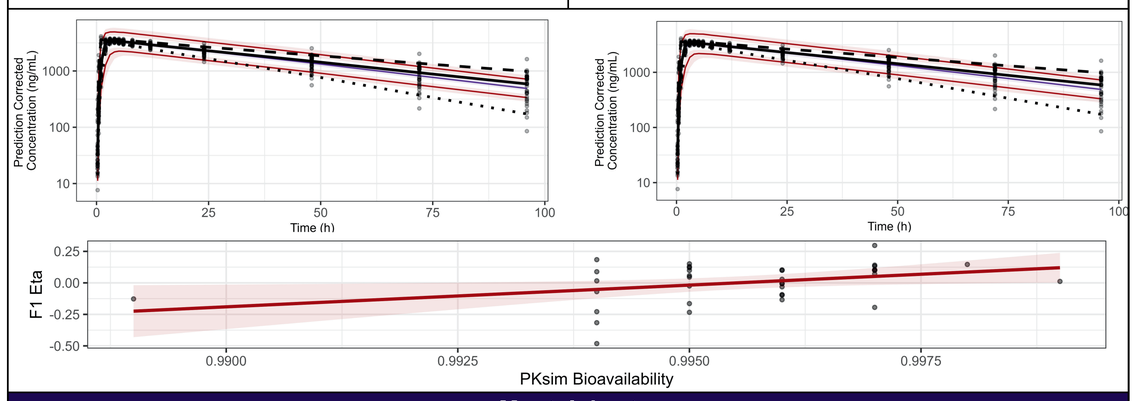
Parallel ZO-FO, absorption, 1 cmt, IIV on CL/F, V/F and F (total), no block. OFV=-1125.923




**Fluconazole**

Sequential ZO-FO-FO absorption, 1 cmt, IIV on D1. OFV=-778.115

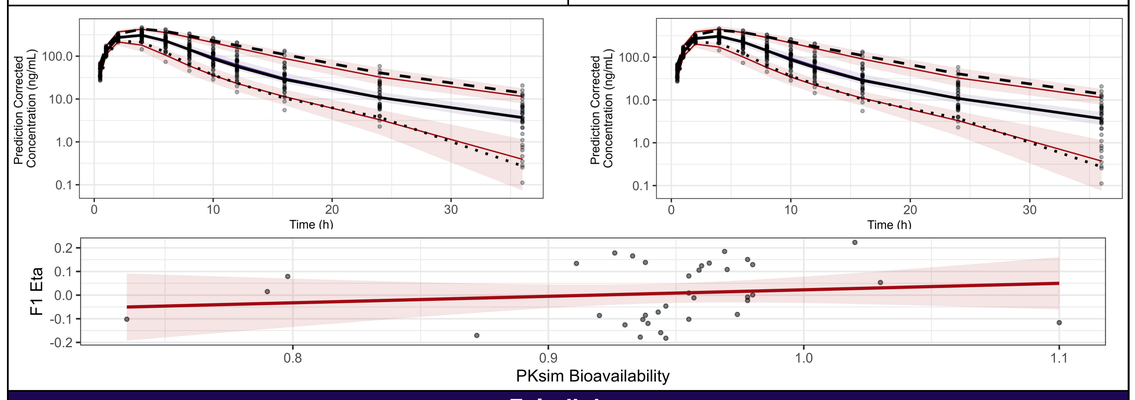
Sequential ZO-FO-FO absorption, 1 cmt, IIV on D1 and F1. OFV=-914.589




**Montelukast**

Sequential ZO-FO absorption, 2 cmt, IIV on L/F, Q/F and V3/F, full block. OFV=-812.646

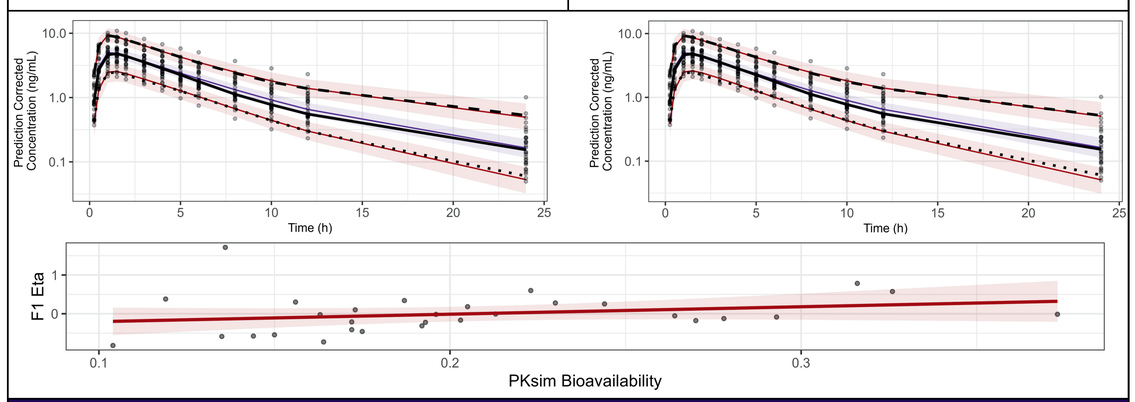
Sequential ZO-FO absorption, 2 cmt, IIV on CL/F, Q/F and V3/F, full block, and IIV on F1. OFV=-870.345




**Felodipine**

Sequential ZO-FO absorption, 2 cmt, IIV on CL/F, V2/F and Ka, full block. OFV=-1190.019

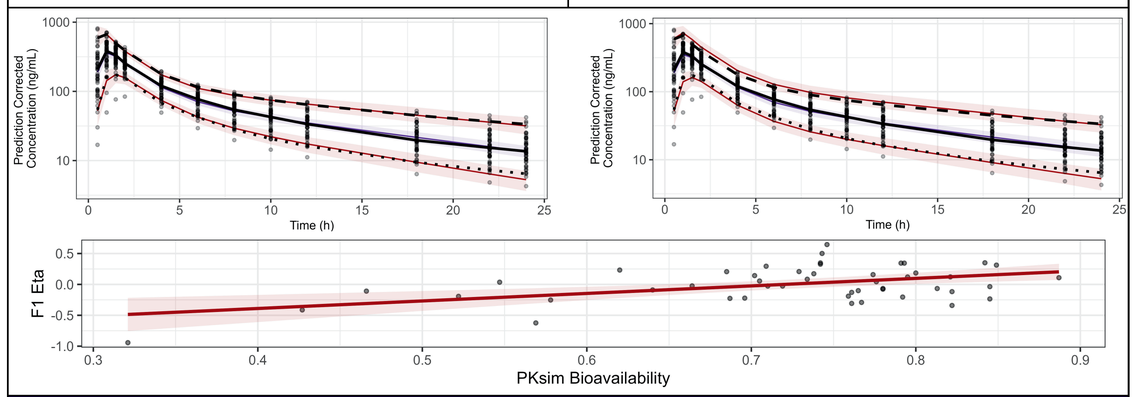
Sequential ZO-FO absorption, 2 cmt, IIV on CL/F, V2/F, Ka and F1, full block. OFV=-1694.553




**Dapagliflozin**

Sequential ZO-FO absorption, 2 cmt, IIV on CL/F, V2/F, D1 and Ka, full block. OFV=-1533.749

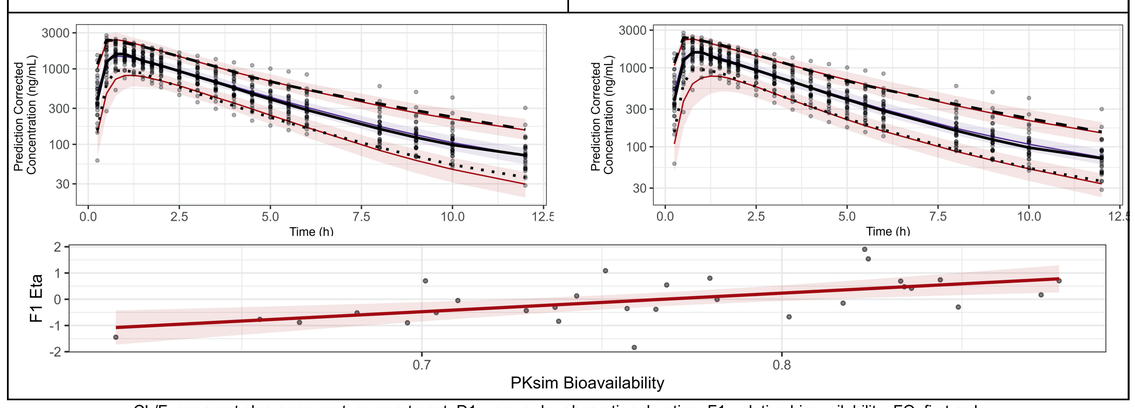
Sequential ZO-FO absorption, 2 cmt, IIV on CL/F, V2/F, D1, Ka and F1, full block. OFV=-1921.191




**Cimetidine**

Sequential ZO-FO absorption, 2 cmt, IIV on CL/F, V2/F and Ka, full block. OFV=-1774.47

Sequential ZO-FO absorption, 2 cmt, IIV on CL/F, V2/F, Ka and F1, full block. OFV=-2451.22




CL/F: apparent clearance, cmt: compartment, D1: zero-order absorption duration, F1: relative bioavailability, FO: first-order, IIV: inter-individual variability, OFV: objective function value, V/F: apparent volume of distribution, ZO: zero-order

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