Physiology Based (PB)PK Modelling

Pediatric Extrapolation of Adult Bioequivalence & Fixing dissolution limits

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Scope of Presentation

- Biopharmaceutics Applicability of PBPK
- Product details/Objectives/End Points
- Methodology
  - Origin of data
- Results
- Evidence based opinion

Introduction and objectives

Biopharmaceutics Applications of PBPK

1. **Predict systemic drug exposure**
2. **Perform Virtual Bioequivalence**
3. **Establish dissolution safe space**
4. **Evaluate drug product quality**
5. **Enable regulatory decision making**

References
- M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms. 2023
- The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls, US FDA 2020
- EMA. Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation, 2018

Objectives & End Points of PBPK

Objectives	**<u>EXTRAPOLATE Adolescent population bioequivalence</u>** • from adult bioequivalence data
	<u>ASSESS IMPACT</u> of Dissolution limits due to • formulation-related features (release rates, particle size distribution and disintegration time) • Perform virtual bioequivalence
End Points	• Standard PK end points • Hypothesis: show bioequivalance between test and reference APIs
	• Dissolution safe space range: +/- 10% or larger?

Methodology

Origin of the data

Data	In-House	Literature
Clinical PK & Bioequivalence	Innovator APIs – Adult (fasted and fed) - Paediatric (historical)	Reference API - Adult (fasted & fed) - - Paediatric (historical)
Particle size	Innovator APIs	Reference API
In-vitro dissolution	Available	Derived from particle size, distribution and disintegration time

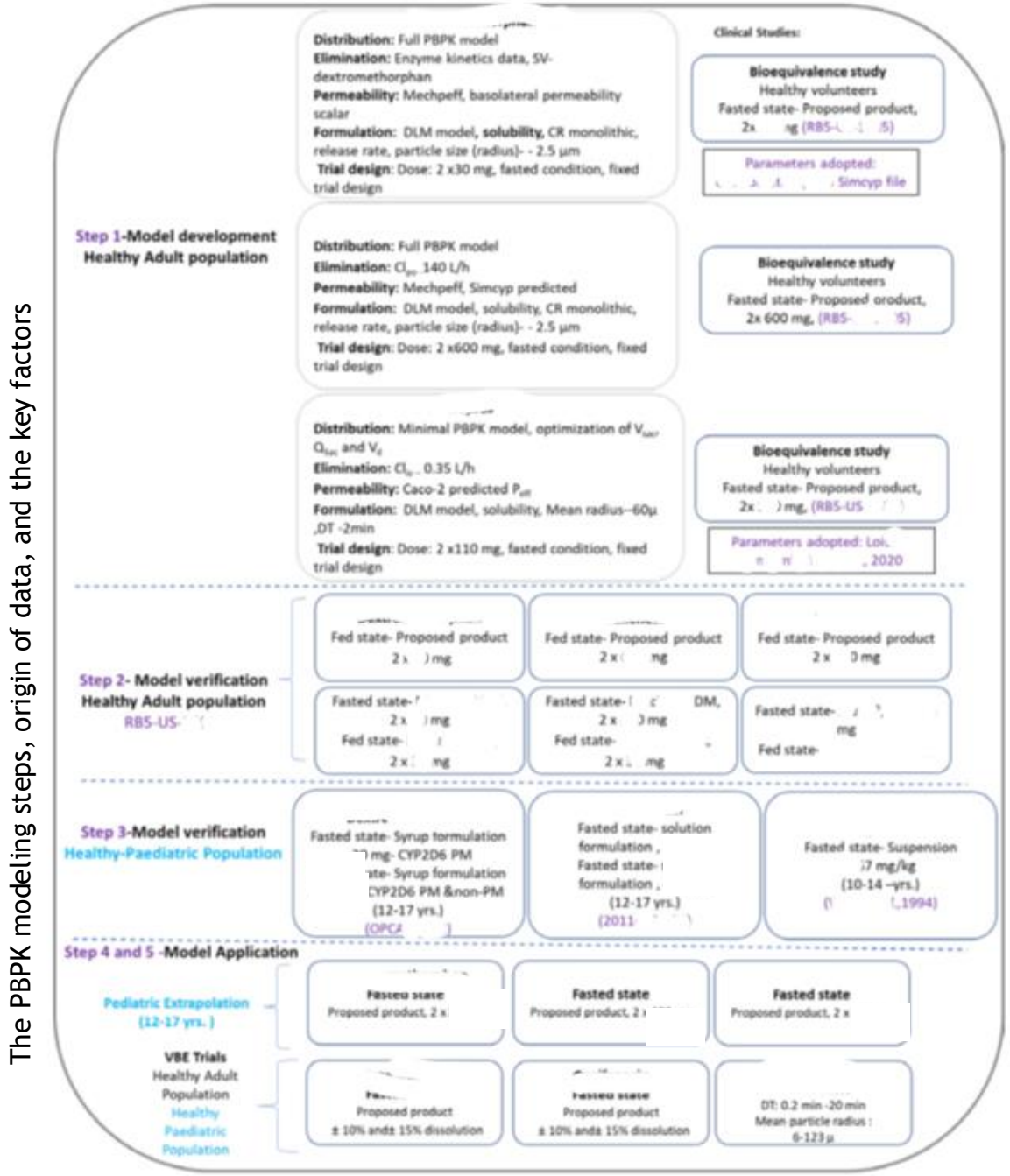
Tool SIMCYP software

- Version 21 of the Simcyp Population-Based Simulator
- Full body Model
- Minimal model
  - Absorption, Distribution and Metabolism
    - Couple of APIs were sensitive to metaboliser status
  - Single adjusting compartment
- Setting key parameters using SYMCIP Simulator

PBPK modelling strategy

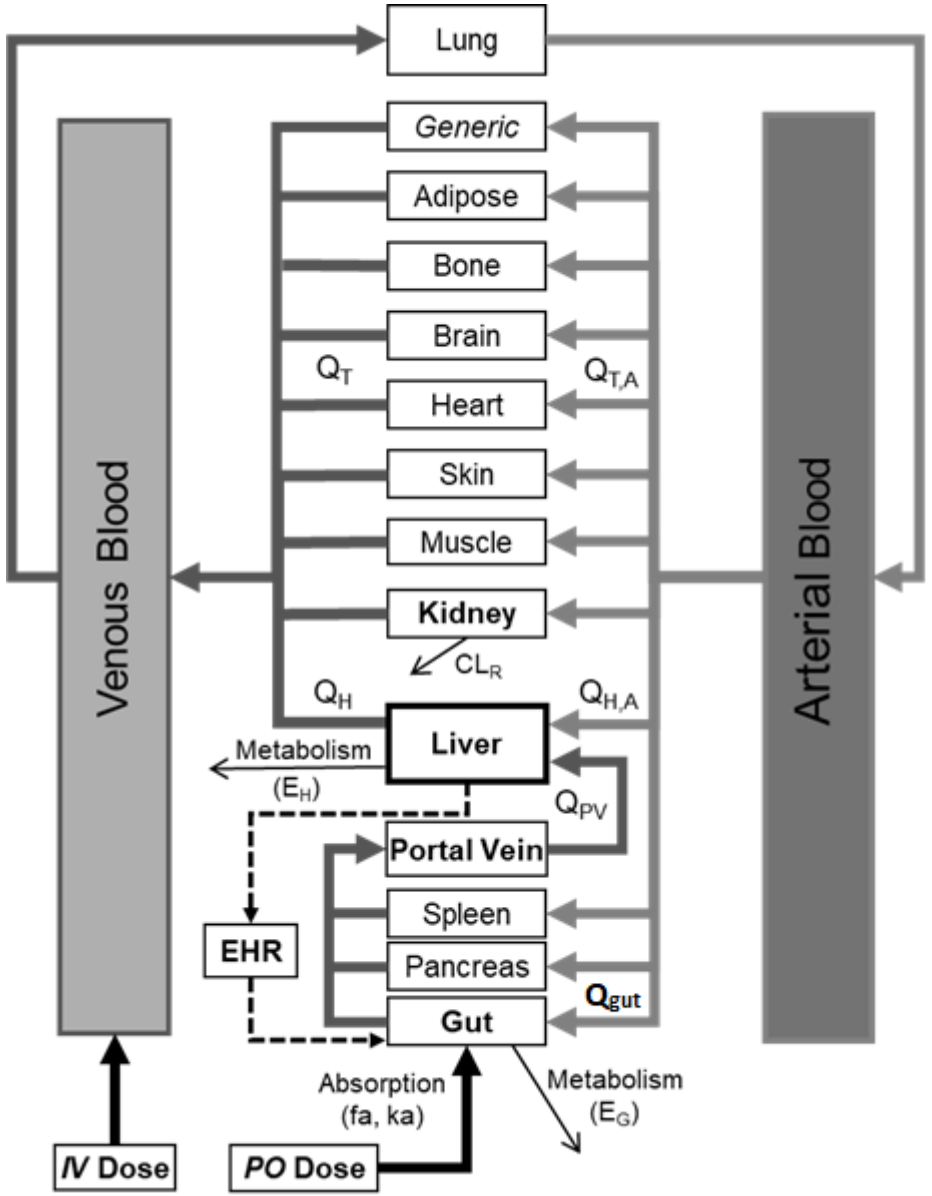
The modeling for this project was divided into three parts:

- 1) model development (step 1),
- 2) model verification (step 2-3) and
- 3) model application (step 4-5).



Full Model for multiple APIs

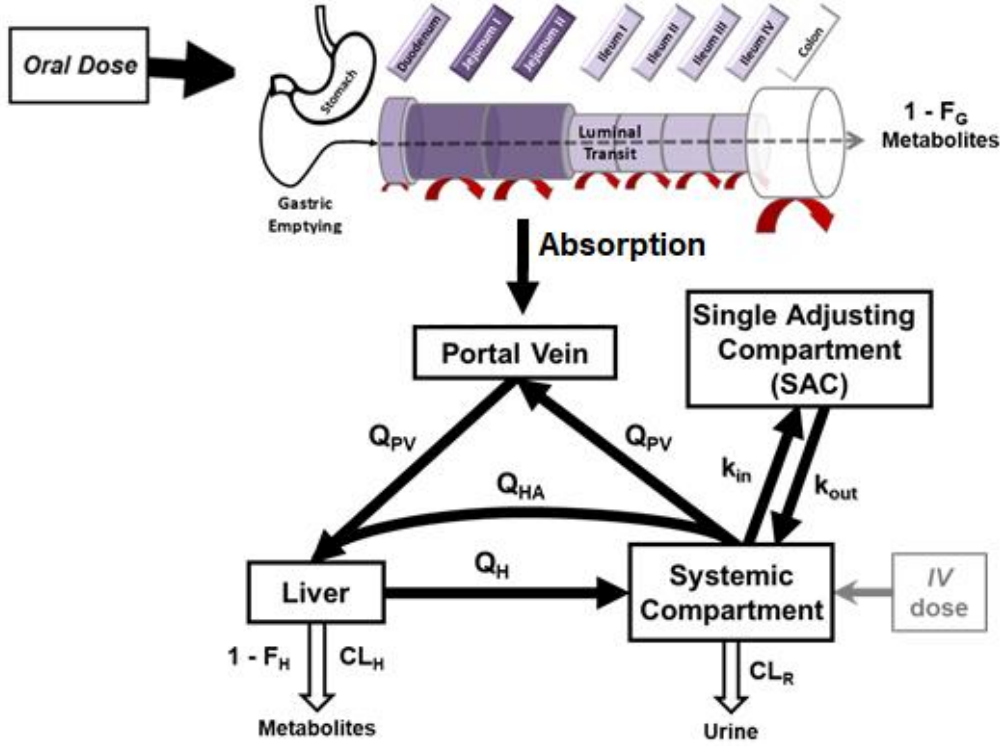
- Full model
  - Incorporate various body compartments
  - each of them display volume, blood flow rate, tissue distribution or metabolic capacity.
  - They are scalable and adjusted for children.
- Physiological parameters are taken from databases or the literature.
- **CYP metabolizer status was tested for applicable APIs**



Minimal Model

Minimal PBPK model

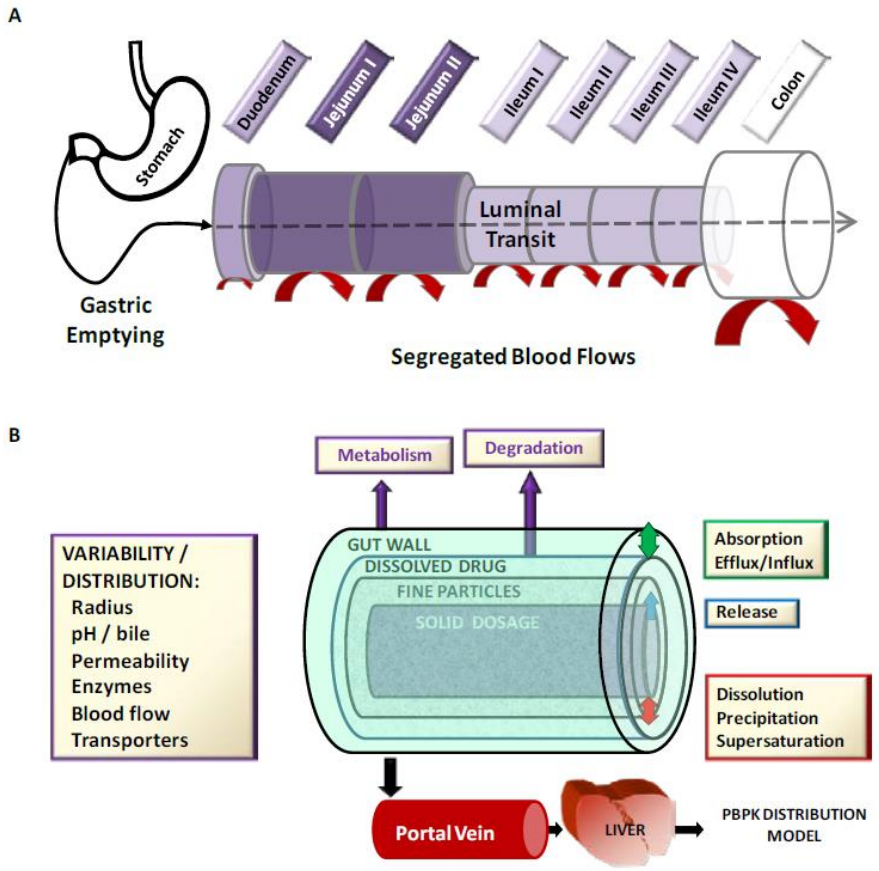
- Single adjusting compartment (SAC)
- GI tract for blood-tissue distribution
  - chosen to predict the distribution for API with low Vd at steady state V_{SS}.
- The estimated physiological parameters were taken from the literature



ADAM model for absorption

- Describes the drug disintegration, dissolution, precipitation, transit, and permeation *via* the gut-wall and metabolism in the gut

- Predicted influence of above and particle size (Log normal distribution assumed) on PK of the drug



Model Verification

- Model verification occurred in two steps.

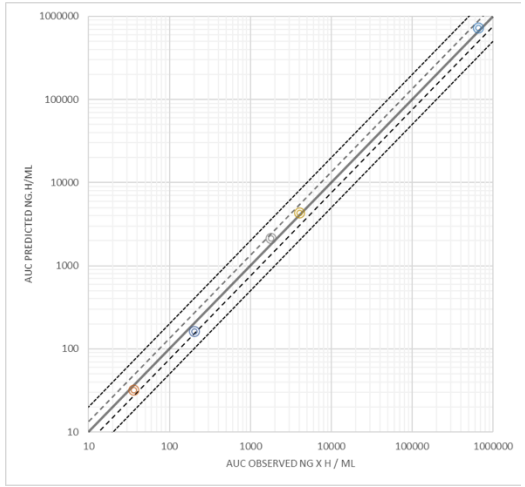
  1. **predictive ability** using Reckitt clinical PK data of the healthy adults from observed clinical bioequivalence trial.
     - The model was verified for both fasted and fed conditions.
  2. predictive ability in adolescents using single dose PK data
     - at different dose levels of the various API

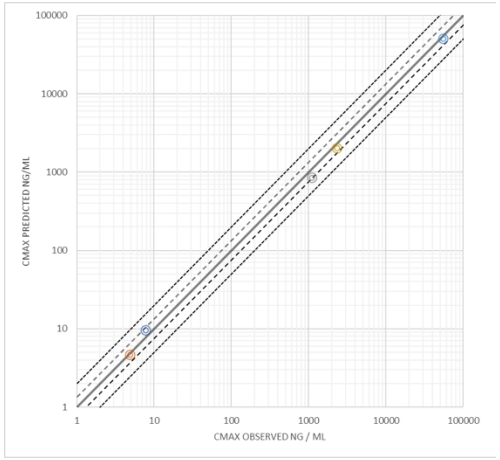
Results

Model verification in adult subjects

1. Validation was performed for the multiple APIs
   - for Cmax and AUC using 0.8-1.25 as limits of acceptance
2. The simulated data overlaid the observed data.
   - The verification of the PBPK model in adults
3. The above confirms acceptability of model for pediatric PK verification

Adults Observed (dots) Log Linear PK & Simulated (lines) with Confidence intervals



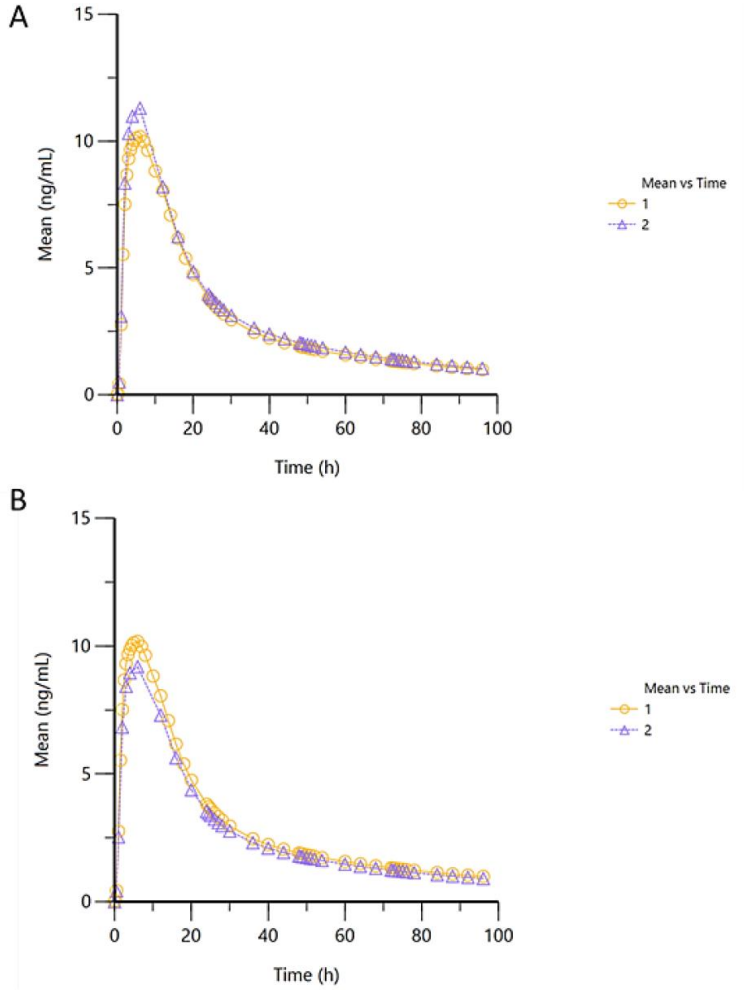


PBPK model application 1- pediatric extrapolation

- Simulated the PK of a single oral dose of FDC tablets in adolescents 12 to 17 years of age
  - *Confirmed the equivalence of the monocomponents in Innovator to the reference FDC formulation*
- Overall confirmed the ability of the model to extrapolate adult PK data for the recommended dose to the target pediatric age group

PBPK model application 2 - dissolution limits

- Based on dissolution, disintegration and particle size
  - The risk of inequivalence was calculated
- A safe dissolution space was proposed in order to have a robust formulation
  - +/10%



Example of dissolution influence ± 10% on API 1

Evidence based conclusion and future applicability

For Pediatric Population

- The model verified adult and adolescent PK data
  - Extrapolation of adult PK data to adolescent population +ve
- Reduced the burden of pediatric clinical study
- Confirmed the adequacy of the formulation and doses
- Enabled acceptance of data in regulatory decision making
  - Reanalysis of data by regulators was possible

For Industry

- A useful tool for investigating and testing critical quality attributes of drug products
  - Defining acceptance limits
  - Ensured meaningful quality of final products

- Exploring opportunities
  - pharmaceutical drug product development
  - Manufacturing changes and controls