

Toward Personalized Salbutamol Therapy: Validating Virtual Patient-Derived Population Pharmacokinetic Model with Real-World Data

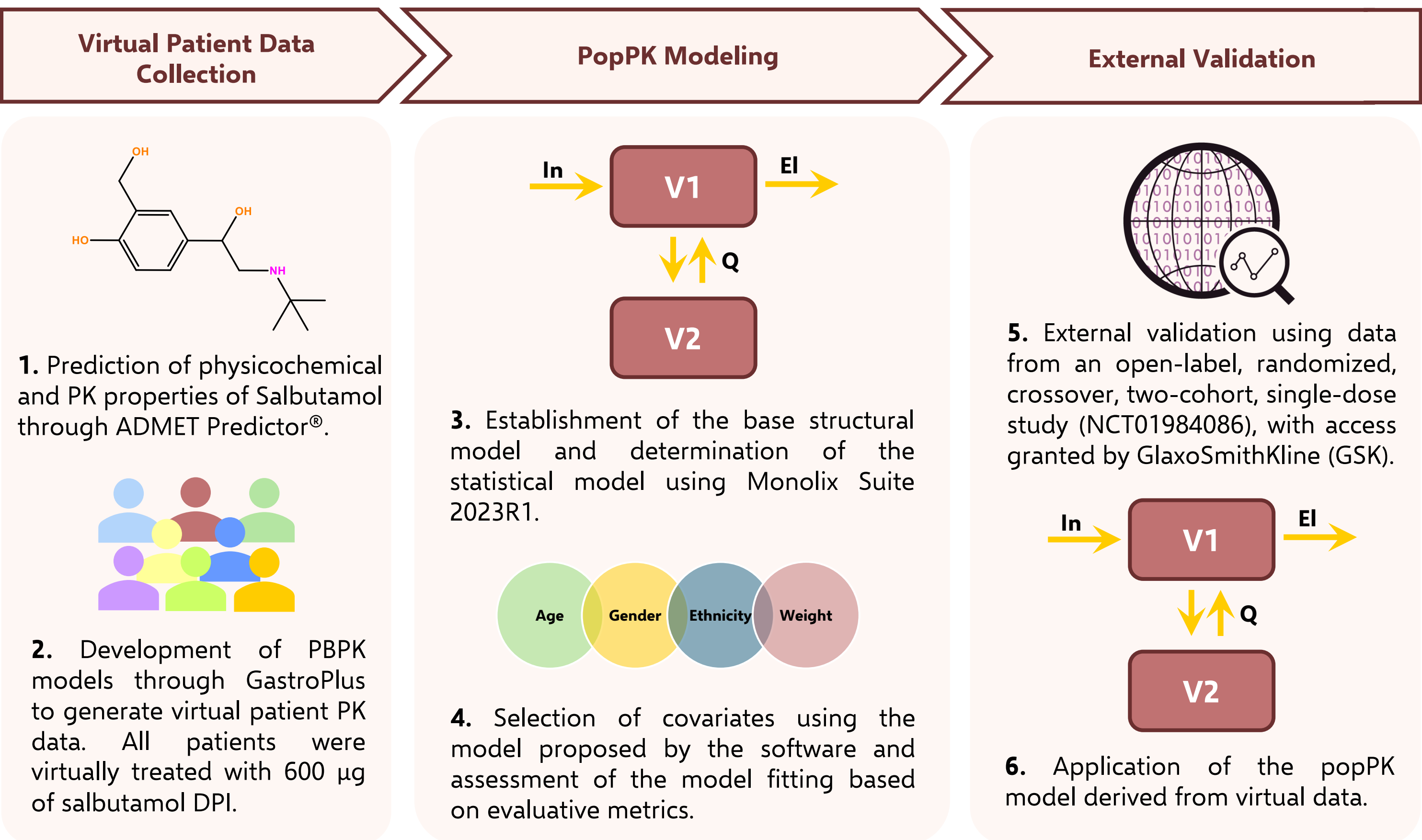
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Introduction

Individual factors such as age, weight, body mass index (BMI), gender, race, genetics, smoking, and dietary habits, can contribute to variations in drug disposition [1,2]. Population pharmacokinetic (popPK) modelling is essential for identifying measurable factors affecting dose-concentration relationships, and tailoring dosage regimens to improve therapeutic outcomes [3]. Salbutamol, a short-acting β_2 -agonist (SABA), used in asthma treatment, requires study due to its continued prescription despite not being recommended as monotherapy [4,5]. In this study, a popPK model for salbutamol delivered via dry-powder inhaler (DPI) was developed to identify key patient characteristics that influence treatment response. Additionally, it demonstrated the feasibility of using synthetic data from physiologically-based pharmacokinetic (PBPK) models to develop the popPK model, as PK data of salbutamol is scarce. External validation using real patient data tested the model's predictive performance, highlighting the potential of virtual patient modeling in advancing this field.

Workflow



External validation using real-world data

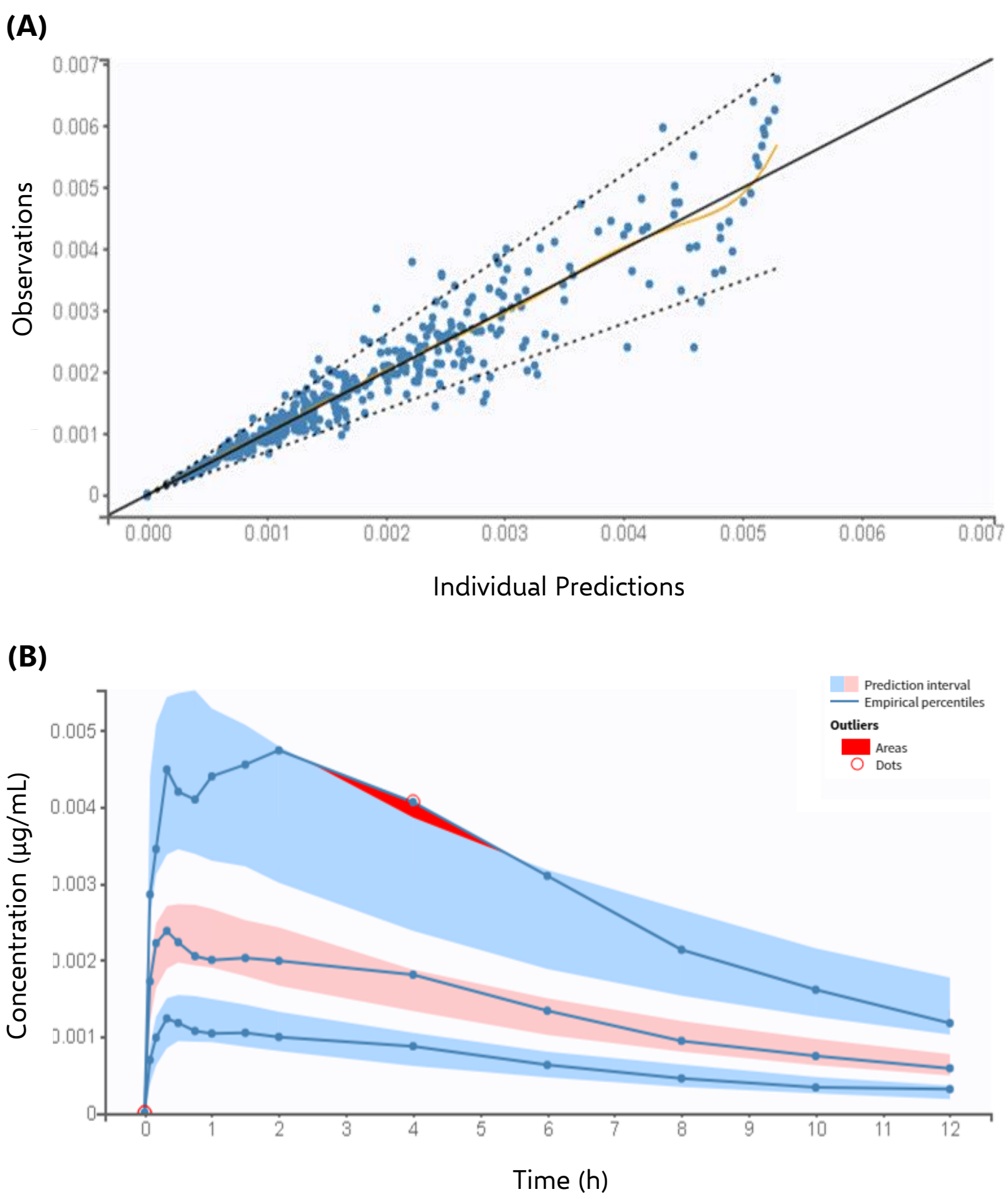


Figure 3. Goodness-of-fit plots of the final popPK model. (A) Observed salbutamol concentration vs individual predictions using conditional mode (EBEs) for the two-compartment model with first-order absorption, no delay, and linear elimination applied to the clinical study dataset for external validation; and (B) The VPC of the final covariate PK model, displaying the prediction intervals for the 10th, 50th, and 90th percentiles (shaded areas, from bottom to top, respectively). Outliers are visualized as red dots and areas.

The model derived from the virtual dataset was found to fit the data from the GSK-sponsored clinical trial. Despite a proportion of outliers of **7.62%**, the model is considered **suitable** for the data. Thus, by validating the model developed from synthetic data with real-world data, this methodology can be employed in therapeutic regimen optimization studies. Its advantages are evident, including **flexibility**, **cost-effectiveness**, and the ability to simulate an **heterogeneous population**.

Conclusions

Our study addresses critical challenges in popPK modeling, particularly regarding data **scarcity**, **incompleteness**, and **homogeneity** in traditional clinical trials. By leveraging synthetic data derived from PBPK modeling, we have overcome these limitations and provided insights into salbutamol PK profile across diverse patient populations. We have identified **significant associations between individual characteristics and salbutamol's PK parameters**, highlighting the importance of personalized therapeutic regimens in achieving optimal treatment outcomes.

PopPK modeling using virtual data patient

Table 1. Patient demographics (mean or median $\pm$ standard deviation, SD or interquartile range, IR) from virtual dataset and clinical trial. In both studies, patients received a single dose of 600 µg of salbutamol, delivered via DPI through the inhalation of 3 blisters (200 µg per blister, resulting in a cumulative dose of 600 µg).

Characteristics	Virtual Patients (n = 32)	Clinical Study Patients (n = 30)
Age (years)	20.0 $\pm$ 20.0	26.8 $\pm$ 4.8
Gender (n, %)		
Female	14, 44%	8, 27%
Male	18, 56%	22, 73%
BMI (kg/m ²)	21.3 $\pm$ 6.6	24.7 $\pm$ 3.8
Height (cm)	157.0 $\pm$ 30.0	177.8 $\pm$ 9.5
Weight (kg)	50.4 $\pm$ 21.9	78.9 $\pm$ 17.6
Race (n, %)		
American Indian or Alaskan Native	12, 38%	1, 3%
East Asian	20, 62%	ND
Mixed Race	ND	2, 7%
Caucasian	ND	27, 90%

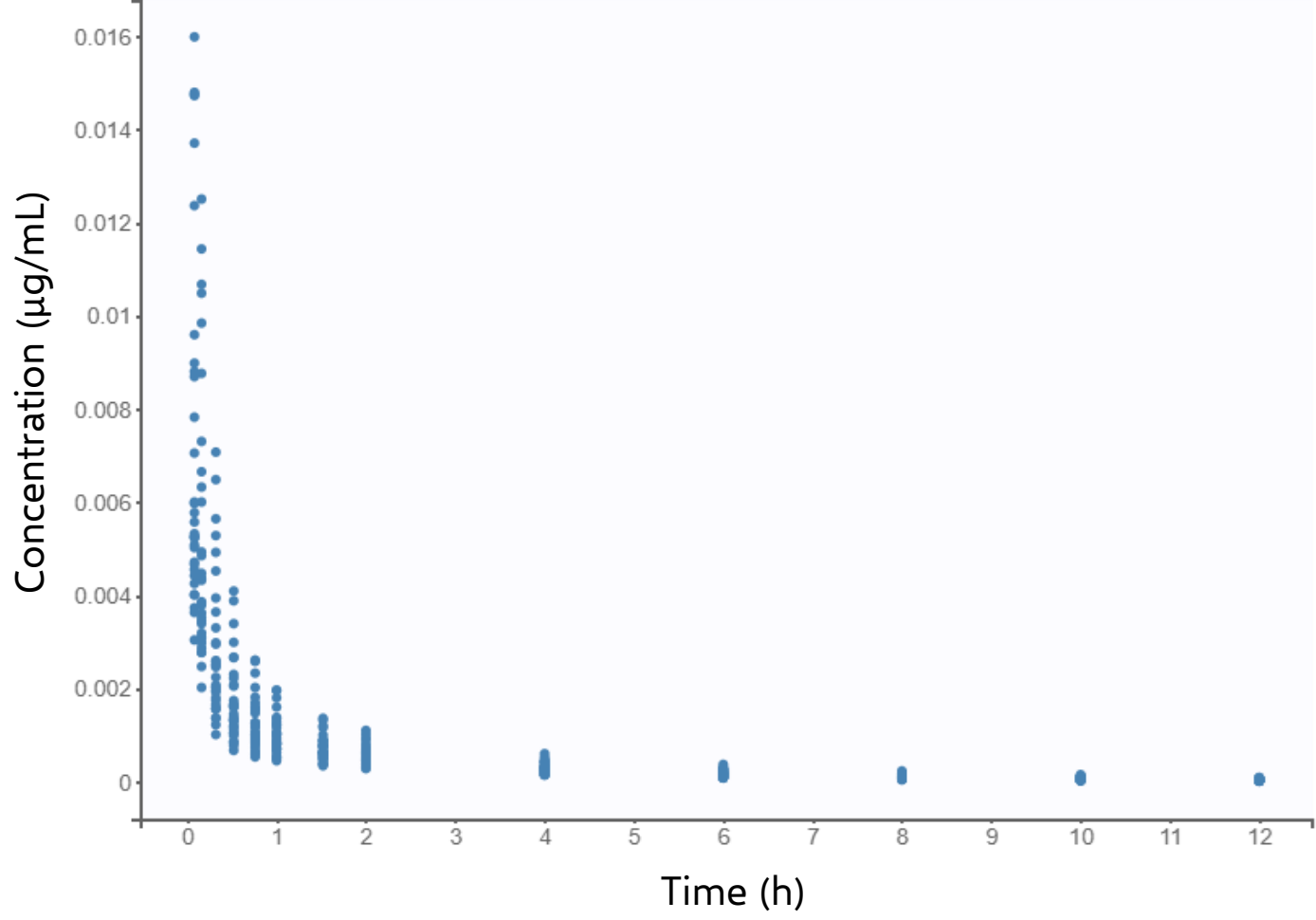


Figure 1. Time-course of salbutamol plasma concentrations. Following inhalation administration of 600 µg of salbutamol (3 successive inhalations of 200 µg) in DPI form.

The plasma concentration-time profiles of salbutamol DPI were best described by a **two-compartment model**, with **first-order absorption** (no lag time), and **linear elimination**. A -2 loglikelihood (LL) of **-6910.06** and a corrected Bayesian Information Criterion (BICc) of **-6808.94** were obtained. All structure parameters were estimated with good precision, with relative standard error (RSE) < 30% for fixed effects.

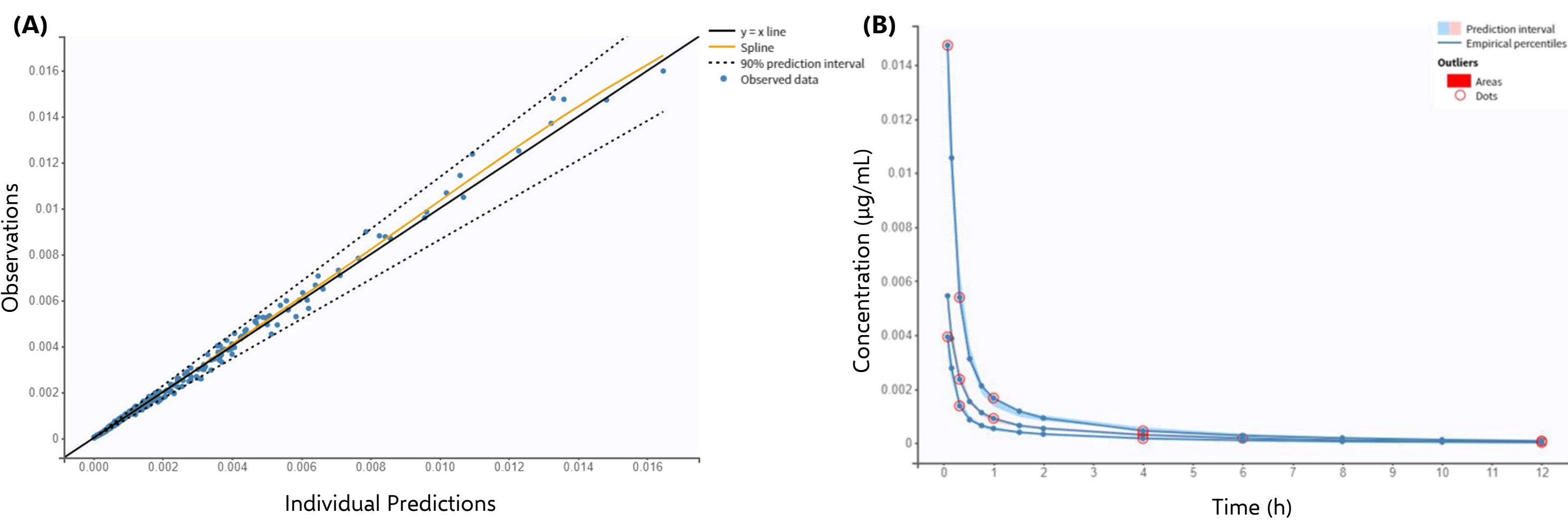


Figure 2. Goodness-of-fit plots of the final popPK model. (A) Observed salbutamol concentration vs individual predictions using conditional mode (EBEs) for the final popPK model; and (B) The VPC of the final covariate PK model, displaying the prediction intervals for the 10th, 50th, and 90th percentiles (shaded areas, from bottom to top, respectively). Outliers are visualized as red dots and areas.

Impact of covariates on salbutamol PK parameters

The developed model revealed the influence of covariates on the PK parameters of salbutamol.

Age has a significant impact on Cl and Q

Gender influences k_a and Cl

Race has an impact on Cl

Weight has a considerable influence on Cl, Q and V2

Acknowledgments:

This research was financed by Fundo Europeu de Desenvolvimento Regional (FEDER) funds through the COMPETE 2020 Operational Programme for Competitiveness and Internationalisation (PO-CI), Portugal 2020, and by Portuguese funds through Fundação para a Ciência e a Tecnologia (FCT) in the framework of projects IF/00092/2014/CP1255/CT0004 and CHAIR in On-co-Innovation from Faculty of Medicine, University of Porto (FMUP). This publication is based on research using data from GlaxoSmithKline that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication.

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