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PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELLING APPROACH FOR CLINICAL RESEARCH ON TACROLIMUS

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ABSTRACT

Tacrolimus is an effective immunosuppressant that reduces the risk of organ transplant rejection. Despite being the drug of choice, there are numerous challenges such as the narrow therapeutic index, high pharmacokinetics and pharmacodynamic variability, drug and food interactions etc. associated with its use. Therefore, model-informed drug development becomes essential to support such drugs at different stages of research and clinical application. This review highlights the need for physiologically based pharmacokinetic (PBPK) modelling in the research and development of drugs like Tacrolimus. The applications of PBPK to evaluate drug-drug interactions, facilitate first-in-human dose estimations, drug-food interactions, biopharmaceutical risks, selection of suitable drug candidates based on biopharmaceutical properties, requirement of fasting and fed state for bioequivalence study, clinical study waivers for lower strengths, critical bioavailability attributes, impact of demography, and to support regulatory filings etc. have made this approach a building block of drug research and development.

KEYWORDS: Tacrolimus, Pharmacokinetics, Pharmacodynamics, Drug Interactions, PBPK, Model informed drug development.

1. INTRODUCTION

Tacrolimus being profoundly effective immunosuppressant that reduces the risk of organ transplant rejection, has got multiple challenges associated with its use. It has got the rare combination of narrow therapeutic window and high pharmacological variability

(pharmacokinetic [PK] and pharmacodynamic [PD].[1] It should be noted thus, treatment with tacrolimus can cause adverse reactions such as nephrotoxicity and neurotoxicity due to overdose and transplant rejection due to low dose.[2] Uptake of Tacrolimus from the digestive system after oral intake is incomplete and inconsistent. The total availability in grown kidney transplant individuals is 17±10%; in adult liver transplant cases is 22±6%; in well individuals is 18±5%.[3] Having lower bioavailability and the risk associated with the systemic concentration, it is essential to understand the impact of the concomitant administration of various substances, such as drugs, dietary supplements and nutrients, on the pharmacokinetics of tacrolimus.[2] Therefore, model informed drug development becomes essential for such drugs. Generally, the focus of model informed drug development is to make use of novel modelling and simulation tools to support drug discovery and development through various multiple applications. In recent years, modelling and simulation-based approaches have been used for the development of both new chemical entities (NCE) and generic products.[4,5] The range of applications of modelling and Simulation (M&S) solely depend on the development stage of the drug. For NCE's, M&S could be applied to evaluate drug-drug interactions, facilitate first-in-human dose estimations, drug-food interactions, assess biopharmaceutical risk with bridging of formulation between various phases of clinical trials, and selection of suitable drug candidates based on biopharmaceutical properties, etc.[4-6] The applications for generic products include; risk assessment for the conduct of bioequivalence (BE), assessment of fasting and fed state, clinical study waivers for other strengths, identification of critical bioavailability attributes, impact of demography, and to support the BE studies for regulatory filings that differ from the recommended.[4] The ultimate aim of all the model-based approaches is to reduce the timelines of drug launch in the market especially for generic products. The commonly used modelling and simulation-based approaches are physiologically based pharmacokinetic modelling (PBPK), physiologically based biopharmaceutics modelling (PBBM) and Population Pharmacokinetics.

2. PBPK MODELLING

A mathematical framework known as PBPK model enables to mimic the pharmacokinetics of drugs on the basis of an interaction of biological, physicochemical and metabolic properties and factors.[7] PBPK models and other pharmacokinetic models can be constructed primarily from observable experimental data (a "top down" approach) or from a more comprehensive understanding of the human body and its mechanisms (a "bottom up" approach)[8] The compartments of PBPK models which depict the various physiological organs of the body are

connected by the circulating blood system. Specific to the species of interest, each compartment has tissue volume and blood flow rates that precisely characterize it. Every tissue is described based on either perfusion-rate-restricted or permeability-rate-restricted.[9]

Physiologically based pharmacokinetic (PBPK) modelling plays a crucial role in optimizing the use of tacrolimus, a calcineurin inhibitor with a narrow therapeutic index and high interindividual variability. The model enables prediction of drug exposure in diverse clinical scenarios, accounting for factors like CYP3A5 polymorphism, co-administered drugs, and demographic variability. It supports dose individualization, especially in special populations like paediatric and transplant patients. Furthermore, PBPK models assist in evaluating the impact of drug-drug interactions (DDIs) and first-pass metabolism, improving therapeutic outcomes while minimizing adverse effects. A semi-physiologically based population pharmacokinetic (semi-PBPK) model was constructed and an online dashboard to personalize tacrolimus dosing in Chinese adult liver transplant patients co-administered with voriconazole.[10] The model incorporated dynamic CYP3A inhibition and patient-specific covariates, including body-mass index (BMI) and postoperative days, to optimize therapy in the context of drug-drug interactions. Van der Veken et al. (2023)[11] constructed a full PBPK model integrating CYP3A4 ontogeny, red blood cell binding, and age-specific absorption to describe tacrolimus disposition in paediatric kidney transplant recipients, identifying blood partitioning as a key determinant of pharmacokinetic variability. **Pei et al. (2023)[12]** formulated a 15-compartment PBPK model to optimize tacrolimus dosing in adult heart transplant patients, identifying CYP3A53, CYP3A418B, and IL-10 G-1082A polymorphisms as significant predictors of drug exposure and demonstrating the impact of voriconazole co-administration. PBPK modelling was applied to pregnant populations, highlighting the limitations of dose adjustments based solely on total tacrolimus concentrations, as free drug levels remained more stable than total levels despite altered plasma protein binding.[13] **Hong et al. (2023)**[14] investigated the drug-drug interaction between ivacaftor and tacrolimus in lung transplant recipients using PBPK simulations, revealing a 2.36-fold increase in exposure due to CYP3A inhibition and recommending a 50% dose reduction. He et al. (2022, 2021)[15,16] used PBPK models to characterize the inhibitory effects of Wuzhi capsule components (schizandrol A/B, schisantherin A, schisandrin A) on CYP3A-mediated tacrolimus metabolism, predicting genotype-dependent increases in exposure (up to 2.70-fold) and emphasizing caution in herbal co-administration. Guan et al. (2024)[17] developed age-specific PBPK models in pediatric HSCT patients, adjusting for CYP3A4/3A5 ontogeny

and recommending genotype-specific tacrolimus doses to account for reduced enzyme expression and clearance in younger children. Xu et al. (2025)[18] focused on PBPK modeling in infected pregnant women, incorporating inflammatory mediators like IL-6, and proposed trimester-specific tacrolimus dose adjustments based on trough level simulations. Karakitsios et al. (2025)[19] evaluated amorphous solid dispersion (ASD) formulations of tacrolimus using in vitro dissolution and PBPK modeling, demonstrating accurate prediction of bioequivalence and aiding early formulation screening. Martischang et al. (2024)[20] simulated continuous IV infusion scenarios in transplant patients unable to tolerate oral tacrolimus, providing Css/Cmin-based conversion ratios and validating them in clinical settings. El-Khateeb et al. (2023)[21] integrated PBPK modelling and therapeutic drug monitoring to assess the impact of chronic kidney disease on tacrolimus clearance, showing a 36% reduction in intrinsic clearance correlated with declining eGFR. Adiwidjaja et al**.** (2020)[22] explored PBPK-predicted interactions between Schisandra sphenanthera lignans and TKIs, showing significant CYP3A4-mediated interaction with bosutinib, but minimal effect on imatinib. Maruyama T et al. studied drug-drug interaction simulated between letermovir and extended-release tacrolimus in Japanese renal transplant patients, recommending genotype-guided dose reductions (57–65%) based on predicted increases in tacrolimus exposure.[23]

2.1. Basics to develop a PBPK Model

The whole-body PBPK model identifies the organs responsible for drug absorption, distribution, excretion, and metabolism based on their physiological function or volume.[24] These include the heart, lungs, brain, stomach, spleen, pancreas, gut, liver, kidney, gonads, thymus, adipose tissue, muscle, bone, and skin. The arterial and venous blood compartments connect the tissues, and each has its own blood flow rate, volume, tissue partition coefficient, and permeability.[25] It assumes or defines that each tissue is either permeability-limited or perfusion-limited. Perfusion-rate-limited kinetics are commonly observed in small lipophilic molecules where the limiting process for absorption is blood flow to the tissue. The limiting process of absorption for larger and more hydrophilic molecules is permeability across the cell membrane.[26]

A compartment is defined as a region with uniform distribution, where a sample is representative of the entire compartment.[27] Blood represents the central compartment that connects to one or two peripheral compartments via rate constants in a classical PK model.[28] PBPK is a compartmental model in which the volumes of the compartments match the actual

physical volumes of the organs and tissues and the compartments represent actual tissue and organ spaces.[29] One significant advantage of PBPK modelling is the availability of a detailed structural representation of an organism's physiology. The different parameters required for a model either collected from literatures or computed using precise and thoroughly verified formulas or from existing knowledge. However generally speaking it is possible to differentiate between the drug parameters and the organism parameters.[25]

2.2. Modelling strategy

PBPK models use data from in vitro experiments as well as in vivo preclinical and clinical data, as opposed to traditional data-fitting pharmacokinetic models that take a "top down" approach and "bottom up" approaches that advocate modelling entirely in virtual space. Kostewicz et al. classified PBPK modelling as a "middle out' approach, where the model is built in an iterative manner. During the drug development process, the model is redefined as the in vitro and/or in vivo data becomes available.[30] The basic information required for model development can be divided into organism related, drug related and administration protocol and formulation related.[25]

2.3. Model development

Khalil F. et al. divided PBPK model development into five major steps: (1) specifying general model structure, (2) specifying tissue model, (3) writing model equations, (4) defining model parameterisation, and (5) simulations and/or parameter estimation.[31]

2.3.1. General Model Structure Specification

The different organs and tissues are depicted in PBPK models as compartments connected by a blood circulation loop that is separated into arterial and venous pools simulating the structure of the living organism under study. The natural basis for compartment selection is the body’s overall physiology and anatomy from the cellular level to the whole organism. The number of body regions or compartments needed is not determined by this though because crucial elements of the drugs pharmacokinetic events need to be evaluated. The objective of model together with pharmacological (transport mechanism site[s] of action) and physicochemical (binding lipid solubility and ionization) characteristics of the drug influences the decision.[32] Tissues with similar physiological, physicochemical, and biochemical properties are combined into one compartment, whereas tissues with distinct properties—such as the liver, where metabolism occurs, or target tissues—are separated from the lumped compartments. Finally, PBPK models differ, ranging from partial-body PBPK

models, which include specific body systems or tissues, to whole-body PBPK models, which include almost all body tissues and are represented as separated or lumped compartments.[31]

2.3.2. Tissues/Organs Model Specification

The model for each specific tissue or organ must then be stated. The vast majority of PBPK models have one to four compartments per tissue or organ. The compartmentalisation decision is based on existing information about tissue kinetics and the biochemical process involved once the drug enters the tissue. Each tissue is well-defined under the assumption that it is either perfusion- or permeability-limited.[33] Small molecules of lipophilic nature typically exhibit perfusion-rate-limited kinetics, which limits the process of absorption due to blood flow to the tissue. For more hydrophilic and larger molecules, the factor limiting process of absorption is permeability across the cell membrane.[25]

2.3.3. Writing the PBPK Model Equations

The PBPK model equations are based on the law of mass action, which means they are mass balance equations because kinetic processes are mass transfer phenomena. In PBPK models four different mathematical descriptions of the tissues have been used.[31,34,35] (i) algebraic descriptions, (ii) linear ordinary differential, (iii) nonlinear differential, and (iv) partial differential. Algebraic descriptions are used when the processes are considered to equilibrate instantly and can be static (e.g., alveolar and inhaled air concentrations. Linear ordinary differential are the most commonly used descriptions in describing dynamic pharmacokinetic processes. The nonlinear differentials represent non-linear processes within a specific tissue (e.g., concentration-dependent binding and/or clearance) and the partial differentials are used with the dispersion tissue model.[31]

2.3.4. PBPK-Model Parameterization

Once model equations have been written, the parameters must be specified and/or estimated. The parameters for incorporation into PBPK models are typically physiological or compound dependent.[31] Physiological parameters such as organ/tissue volumes cardiac output and blood flows tissue composition surface area pH values and/or gastrointestinal transit times characterize the anatomical structure and physiological functions of the species under model. These parameters' values have been shown to vary across species and subjects, as well as with age and physiological/pathological state. The second set of parameters needed for a PBPK model depends on the compound and includes data like substance partitioning between body tissues and the blood/plasma (KpT) and permeability—surface area products (P × SA).

These parameters can be obtained through in vitro experiments, extrapolation of experimental in vivo values from animals to humans, or estimation/prediction via specific algorithms.[31]

2.3.5. PBPK Modelling Software for Simulation and Parameter Estimation

After the system is coupled, the model equations are coded in a particular software language for simulation and/or parameter estimation.[31] Commercial platforms like GastroPlus (Simulations Plus, Lancaster, PA), SimCyp (SimCyp, Sheffield, UK), and PK-Sim and MoBi (Bayer Technology Services, Leverkusen, Germany) have made it easier to use complex PBPK models. These commercial PBPK modelling platforms offer a generic model structure for studying the physiology of predefined species and populations. These models use physiological databases, compound-specific information, and biometric data to create a whole-body PBPK model.[25]

2.4. PBPK Modelling approach for Tacrolimus

Tacrolimus having numerous challenges associated with its pharmacokinetics (PK) and pharmacodynamics (PD), PBPK model-based approach could be used in different ways to reduce and overcome these challenges. Some of the aspects for which PBPK has been used for Tacrolimus are as follows.

2.4.1. Food-Drug Interaction

Due to narrow therapeutic window, dose dependent toxicity and pharmacological variability, studies on interaction of tacrolimus with food intake are critical.[2] Helena et al. demonstrated the impact of food intake on tacrolimus PK (food–drug interactions) by developing a PBPK model on PK-Sim® Version 10 using a total of 37 whole blood concentration–time profiles of tacrolimus and incorporated the metabolism via CYP3A4 and CYP3A5, with varying activities used for different CYP3A5 genotypes and study populations. The model demonstrated good descriptive and predictive performance and successfully predicted the interaction between tacrolimus PK and food intake in healthy individuals.[36]

2.4.2. Drug-Drug Interaction

Tacrolimus is prone to drug–drug interactions, when co-administered with drugs that are metabolized by CYP3A enzymes. Helena et al. demonstrated the impact drug–drug interactions involving the drugs voriconazole, itraconazole, and rifampicin acting as CYP3A perpetrators. PBPK was developed on PK-Sim® Version 10 using a total of 37 whole blood concentration–time profiles of tacrolimus and incorporated the metabolism via CYP3A4 and

CYP3A5, with varying activities used for different CYP3A5 genotypes and study populations.[36]

Maruyama T. and others. also used the PBPK model to illustrate the drug-drug interactions between tacrolimus and letermovir in Japanese renal transplant recipients. Letermovir and extended release tacrolimus PBPK models were created with the Simcyp simulator. A creation of virtual Japanese post-transplant population with physiological parameters specific to Japanese patients, including CYP3A5 genotypes was done. The predictions of the model were accurate for tacrolimus formulations and the model displayed increased tacrolimus exposure due to co-administration with letermovir.[23] **Qian et al.**[10] found that oral phenobarbital significantly reduced tacrolimus levels in pediatric patients more than its intravenous form. Qian et al. used a semi-PBPK model to compare rifampicin's effects on oral versus intravenous CYP3A/P-gp substrates, confirming that DDIs were more pronounced with oral administration. **He et al.**[11,12] explored herb-drug interactions involving Wuzhi capsule constituents (schisantherin A, schisandrin A, and schizandrols), finding that these compounds increased tacrolimus exposure significantly, especially in CYP3A5 non-expressers. **Zhang et al.**[13] highlighted mechanism-based inhibition as the primary factor in these interactions, while **Adiwidjaja et al.**[14] validated PBPK models for Schisandra lignans, warning against co-administration with tacrolimus due to a predicted 2.4-fold increase in drug exposure.

2.4.3. Metabolism and Genetic polymorphism

The another most important factor that affects PK of tacrolimus is metabolism regulated by cytochrome P450 enzymes CYP3A4 and CYP3A5. These enzymes are susceptible to induction or inhibition due to their involvement in the metabolism of a wide variety of drugs.[37]

Guan Y, et al demonstrated the impact of age-related maturation in hepatic and intestinal CYP3A4/3A5 enzymes using physiologically-based pharmacokinetic models. GastroPlusTM (version 9. 0) was used to develop and validate the models in adult volunteers and adult HSCT patients. The models were then extrapolated to paediatric HSCT patients while taking CYP3A4 and CYP3A5 maturation into account. The study highlighted the role of PBPK modelling to explore the age-related maturation of enzymes in children and infants. The findings suggested that elevated tacrolimus levels were due to CYP3A4/3A5 ontogeny

profiles in patients aged 9 months to 3 years and age-adjusted tacrolimus dosing is recommended for children with different CYP3A5 genotypes.[38]

A physiologically based pharmacokinetic (PBPK) model for tacrolimus was created, which included a virtual population that reflects the physiological parameter distributions of renal transplant recipients. The ratios of predicted to observed dose-normalized maximum plasma concentration (C_{max}), 0–12-hour area under the concentration–time curve (AUC 0–12 hours), and trough plasma concentration (C_{trough}) varied between 0.92 and 1.15, demonstrating strong predictive capability. The model quantitatively assessed how cytochrome P450 (CYP)3A4 levels, hematocrit, and serum albumin concentrations, as well as CYP3A5 genotype, influenced the pharmacokinetics of tacrolimus and the variability associated with it. The variation in tacrolimus trough concentrations seen in paediatric patients was predominantly linked to the development profile of CYP3A.[39]

2.4.4. Paediatric Patients and Pregnancy

Van der Veken M. et al. developed a PBPK model to predict adult tacrolimus exposure which was then extrapolated to the paediatric population. Tacrolimus blood plasma partitioning variations in paediatric patients may be a factor in exposure variability according to the study.[11] As discussed above, the PBPK model developed by Guan Y. et al suggested that elevated tacrolimus levels were due to CYP3A4/3A5 ontogeny profiles in patients aged 9 months to 3 years and age-adjusted tacrolimus dosing is recommended for children with different CYP3A5 genotypes.[38] **Xu J. et al.** extended these models to pregnant women with infections, showing that CYP3A5 genotype and IL-6 levels influenced tacrolimus exposure, thereby aiding personalized dosing.[18] Coppola et al. demonstrated that although total tacrolimus levels declined in pregnancy, free drug levels remained stable, highlighting the importance of monitoring free concentrations. **Jogiraju et al.** and **Coppola et al.** further validated the application of PBPK modeling in predicting pregnancy-related pharmacokinetic changes for tacrolimus, with varying degrees of accuracy.[40, 41]

3. CONCLUSION

Modelling and simulations have become an integral part of drug development and are being applied at different stages of research and clinical application. For complex drugs like Tacrolimus with multiple challenges such as narrow therapeutic index, high pharmacokinetics and pharmacodynamic variability, drug and food interactions etc. associated with their use, PBPK modelling is the preferred tool to reduce and overcome these

challenges. The applications of PBPK modelling to evaluate drug-drug interactions, facilitate first-in-human dose estimations, drug-food interactions, biopharmaceutical risks, requirement of fasting and fed state for bioequivalence study, clinical study waivers, critical bioavailability attributes, impact of demography, and to support regulatory filings etc. have made this approach the part and parcel of modern drug research and development. With an appropriate pharmacological and biopharmaceutical knowledge and the availability of required information, PBPK modelling approach can reduce the timelines for a drug product to reach the patients.

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AUTHORS CONTRIBUTION

Sajad Khaliq Dar contributed to the literature search, drafting and finalization of the manuscript. Mohd Akhtar contributed to the finalization and review of manuscript. Arshad H. Khuroo and Ramakrishna Vydana reviewed the final manuscript.

DECLARATION OF CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Woillard J-B, et al., Tacrolimus Updated Guidelines through popPK Modeling: How to Benefit More from CYP3A Pre-emptive Genotyping Prior to Kidney Transplantation, Frontiers in Pharmacology, 8: 358. doi: 10.3389/fphar.2017.00358
2. Miedziaszczyk, M., et al., Controversial Interactions of Tacrolimus with Dietary Supplements, Herbs and Food, Pharmaceutics, 2022; 14: 2154, https: //doi.org/10.3390/ pharmaceutics14102154
3. Budde K, Bunnapradist S, Grinyo JM, Ciechanowski K, Denny JE, Silva HT, Rostaing L, Envarsus Study Group. Novel once-daily extended-release tacrolimus (LCPT) versus twice-daily tacrolimus in de novo kidney transplants: one-year results of Phase III, double-blind, randomized trial. American journal of transplantation, 2014 Dec 1; 14(12): 2796-806.
4. Kollipara S, et al., Industry Perspectives on Implementation of Model Master File (MMF) Framework for Generics and Innovator Drugs: Opportunities, Challenges and Future Outlook, Pharmaceutical Research https: //doi.org/10.1007/s11095-025-03844-0

5. Yuvaneshwari K, Kollipara S, Ahmed T, Chachad S. Applications of PBPK/PBBM modeling in generic product development: An industry perspective. J Drug Deliv Sci Technol, 2022; 69: 103152, https: //doi.org/10.1016/j.jddst.2022.103152
6. Lin W, Chen Y, Unadkat JD, Zhang X, Wu D, Heimbach T. Applications, challenges, and outlook for PBPK modeling and simulation: a regulatory, industrial and academic perspective. Pharmaceutical research, 2022 Aug; 39(8): 1701-31.
7. European Medicines Agency: Reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. https: //www.ema.europa.eu/en/reporting-physiologically-based-pharmacokinetic-PBPK-modelling-simulation (2018). Accessed January 19 2022.
8. Tylutki Z, Polak S, Wiśniowska B. Top-down, bottom-up and middle-out strategies for drug cardiac safety assessment via modeling and simulations. Current Pharmacology Reports, 2016 Aug; 2: 171-7.
9. Zhuang X, Lu C. PBPK modeling and simulation in drug research and development. Acta Pharmaceutica Sinica B., 2016 Sep 1; 6(5): 430-40.
10. Li ZR, Shen CH, Li RD, Wang B, Li J, Niu WJ, Zhang LJ, Zhong MK, Wang ZX, Qiu XY. Individual dose recommendations for drug interaction between tacrolimus and voriconazole in adult liver transplant recipients: a semiphysiologically based population pharmacokinetic modeling approach. European Journal of Pharmaceutical Sciences, 2023 May 1; 184: 106405.
11. Van der Veken M, Brouwers J, Ozbey AC, Umehara K, Stillhart C, Knops N, Augustijns P, Parrott NJ. Investigating tacrolimus disposition in paediatric patients with a physiologically based pharmacokinetic model incorporating CYP3A4 ontogeny, mechanistic absorption and red blood cell binding. Pharmaceutics, 2023 Aug 29; 15(9): 2231.
12. Pei L, Li R, Zhou H, Du W, Gu Y, Jiang Y, Wang Y, Chen X, Sun J, Zhu J. A physiologically based pharmacokinetic approach to recommend an individual dose of tacrolimus in adult heart transplant recipients. Pharmaceutics, 2023 Nov 3; 15(11): 2580.
13. Coppola P, Butler A, Cole S, Kerwash E. Total and free blood and plasma concentration changes in pregnancy for medicines highly bound to plasma proteins: application of physiologically based pharmacokinetic modelling to understand the impact on efficacy. Pharmaceutics, 2023 Oct 13; 15(10): 2455.
14. Hong E, Carmanov E, Shi A, Chung PS, Rao AP, Forrester K, Beringer PM. Application of physiologically based pharmacokinetic modeling to predict drug–drug interactions

between elexacaftor/tezacaftor/ivacaftor and tacrolimus in lung transplant recipients. Pharmaceutics, 2023 May 8; 15(5): 1438.

15. He Q, Bu F, Wang Q, Li M, Lin J, Tang Z, Mak WY, Zhuang X, Zhu X, Lin HS, Xiang X. Examination of the impact of CYP3A4/5 on drug–drug interaction between schizandrol a/schizandrol b and tacrolimus (FK-506): a physiologically based pharmacokinetic modeling approach. International Journal of Molecular Sciences, 2022 Apr 19; 23(9): 4485.
16. He Q, Bu F, Zhang H, Wang Q, Tang Z, Yuan J, Lin HS, Xiang X. Investigation of the Impact of CYP3A5 Polymorphism on Drug–Drug Interaction between Tacrolimus and Schisantherin A/Schisandrin A Based on Physiologically-Based Pharmacokinetic Modeling. Pharmaceuticals, 2021 Feb 27; 14(3): 198.
17. Guan Y, Liu X, Huang K, Wang Y, Qiu K, Wang X, Huang M, Zhou D, Yu X, Zhong G. Physiologically-based pharmacokinetic modelling to investigate the effect of CYP3A4/3A5 maturation on tacrolimus pharmacokinetics in paediatric HSCT patients. European Journal of Pharmaceutical Sciences, 2024 Oct 1; 201: 106839.
18. Xu J, Guo G, Zhou S, Wang H, Chen Y, Lin R, Huang P, Lin C. Physiologically-based pharmacokinetic modeling to predict the exposure and provide dosage regimens of tacrolimus in pregnant women with infection disease. European Journal of Pharmaceutical Sciences, 2025 Mar 1; 206: 107003.
19. Karakitsios E, Angelerou MF, Kapralos I, Tsakiridou G, Kalantzi L, Dokoumetzidis A. Integrating In Vitro Dissolution and Physiologically Based Pharmacokinetic Modeling for Generic Drug Development: Evaluation of Amorphous Solid Dispersion Formulations for Tacrolimus. Pharmaceutics, 2025 Feb 10; 17(2): 227.
20. Martischang R, Nikolaou A, Daali Y, Samer CF, Terrier J. Guidance on Selecting Optimal Steady-State Tacrolimus Concentrations for Continuous IV Perfusion: Insights from Physiologically Based Pharmacokinetic Modeling. Pharmaceuticals, 2024 Aug 8; 17(8): 1047.
21. El-Khateeb E, Chinnadurai R, Al Qassabi J, Scotcher D, Darwich AS, Kalra PA, Rostami-Hodjegan A. Using Prior Knowledge on Systems Through PBPK to Gain Further Insight into Routine Clinical Data on Trough Concentrations: The Case of Tacrolimus in Chronic Kidney Disease. Therapeutic Drug Monitoring, 2022 Apr 4: 10-97.
22. Adiwidjaja J, Boddy AV, McLachlan AJ. Potential for pharmacokinetic interactions between Schisandra sphenanthera and bosutinib, but not imatinib: in vitro metabolism

study combined with a physiologically-based pharmacokinetic modelling approach. British Journal of Clinical Pharmacology, 2020 Oct; 86(10): 2080-94.

23. Maruyama T, Kasai H, Fukaya Y, Shiokawa M, Kimura T, Hamada Y. Drug–drug interactions between letermovir and tacrolimus in Japanese renal transplant recipients simulated using a physiologically based pharmacokinetic model. Frontiers in Microbiology, 2024 Oct 8; 15: 1480874.
24. Peters SA. Physiologically based pharmacokinetic (PBPK) modeling and simulations: principles, methods, and applications in the pharmaceutical industry. John Wiley & Sons, 2021 Oct 12.
25. Kuepfer L, Niederalt C, Wendl T, Schlender JF, Willmann S, Lippert J, Block M, Eissing T, Teutonico D. Applied concepts in PBPK modeling: how to build a PBPK/PD model. CPT: pharmacometrics & systems pharmacology, 2016 Oct; 5(10): 516-31.
26. Brown RP, Delp MD, Lindstedt SL, Rhomberg LR, Beliles RP. Physiological parameter values for physiologically based pharmacokinetic models. Toxicology and industrial health, 1997 Jul; 13(4): 407-84.
27. Upton RN, Foster DJ, Abuhelwa AY. An introduction to physiologically-based pharmacokinetic models. Pediatric Anesthesia, 2016 Nov; 26(11): 1036-46.
28. Gabrielsson J, Weiner D. Pharmacokinetic and pharmacodynamic data analysis: concepts and applications.
29. Aarons L. Physiologically based pharmacokinetic modelling: a sound mechanistic basis is needed. British journal of clinical pharmacology, 2005 Dec; 60(6): 581.
30. Kostewicz ES, Aarons L, Bergstrand M, Bolger MB, Galetin A, Hatley O, Jamei M, Lloyd R, Pepin X, Rostami-Hodjegan A, Sjögren E. PBPK models for the prediction of in vivo performance of oral dosage forms. European Journal of Pharmaceutical Sciences. 2014 Jun 16; 57: 300-21.
31. Khalil F, Läer S. Physiologically based pharmacokinetic modeling: methodology, applications, and limitations with a focus on its role in pediatric drug development. BioMed Research International, 2011; 2011(1): 907461.
32. Bischoff KB. Some fundamental considerations of the applications of pharmacokinetics to cancer chemotherapy. Cancer Chemotherapy Reports, 1975 Jul 1; 59(4): 777-93.
33. Nestorov I. Whole-body physiologically based pharmacokinetic models. Expert opinion on drug metabolism & toxicology, 2007 Apr 1; 3(2): 235-49.
34. Nestorov I. Whole body pharmacokinetic models. Clinical pharmacokinetics, 2003 Aug; 42: 883-908.

35. Nestorov IA, Aarons LJ, Arundel PA, Rowland M. Lumping of whole-body physiologically based pharmacokinetic models. Journal of pharmacokinetics and biopharmaceutics, 1998 Feb; 26: 21-46.
36. Loer HL, Feick D, Rüdesheim S, Selzer D, Schwab M, Teutonico D, Frechen S, van Der Lee M, Moes DJ, Swen JJ, Lehr T. Physiologically based pharmacokinetic modeling of tacrolimus for food–drug and CYP3A drug–drug–gene interaction predictions. CPT: Pharmacometrics & Systems Pharmacology, 2023 May; 12(5): 724-38.
37. Henkel L, et al., Tacrolimus—why pharmacokinetics matter in the clinic, Frontier in Transplantation, 2: 1160752. doi: 10.3389/frtra.2023.1160752
38. Guan Y, et al., Physiologically-based pharmacokinetic modelling to investigate the effect of CYP3A4/3A5 maturation on tacrolimus pharmacokinetics in paediatric HSCT patients, European Journal of Pharmaceutical Sciences, 2024; 201: 106839, https: //doi.org/10.1016/j.ejps.2024.106839
39. Yu M, Liu M, Zhang W, Ming Y. Pharmacokinetics, pharmacodynamics and pharmacogenetics of tacrolimus in kidney transplantation. Current drug metabolism, 2018 May 1; 19(6): 513-22.
40. Jogiraju VK, Avvari S, Gollen R, Taft DR. Application of physiologically based pharmacokinetic modeling to predict drug disposition in pregnant populations. Biopharmaceutics & drug disposition, 2017 Oct; 38(7): 426-38.
41. Coppola P, Kerwash E, Cole S. Use of physiologically based pharmacokinetic modeling for hepatically cleared drugs in pregnancy: regulatory perspective. The Journal of Clinical Pharmacology, 2023 Jun; 63: S62-80.