



Evolution of human pharmacokinetics prediction methods: from allometry to artificial intelligence

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Abstract

Background Accurate prediction of human pharmacokinetics (PK) remains a critical challenge in drug development. Conventional animal-based approaches face inherent limitations due to species differences, driving progress toward more accurate and human-relevant predictive methodologies.

Area covered This review discusses the evolution of human PK prediction methodologies from conventional approaches to emerging technologies. Traditional methods, including allometric scaling, in vitro–in vivo extrapolation, and physiologically based pharmacokinetic modeling, are first examined, with emphasis on their principles, applications, and limitations through representative case studies. Subsequently, emerging approaches, such as artificial intelligence (AI) and machine learning applications, organ-on-a-chip systems, and other advanced in vitro models, are explored. A comprehensive comparison between conventional and AI-based approaches is provided, addressing data requirements, modeling complexity, predictive performance, and practical applicability. Current implementation challenges—including the need for standardization, barriers to cross-method integration, and regulatory considerations—are also discussed.

Expert opinion The future of human PK prediction depends on the strategic integration of complementary methodologies. Conventional methods provide mechanistic transparency, AI-driven approaches offer screening efficiency, and advanced in vitro models deliver physiological relevance. Achieving this integration requires standardized validation frameworks and clear regulatory guidance to support multi-method applications.

Keywords Pharmacokinetics · Allometric scaling · PBPK · IVIVE · Artificial intelligence · Machine learning · Organ-on-a-chip · New approach methodologies (NAMs)

Introduction

Accurate prediction of human pharmacokinetics (PK) has long been recognized as a critical determinant of successful drug development. By bridging preclinical findings with anticipated clinical outcomes, PK prediction supports rational dose selection, safety assessment, and optimization of the therapeutic index. The magnitude of this challenge is underscored by reports from the U.S. Food and Drug Administration (FDA) indicating that nearly 90% of

investigational drugs that appear both safe and effective in preclinical testing fail during clinical development (Sun et al. 2022). A major contributor to this high attrition rate is the inadequate prediction of human PK and absorption, distribution, metabolism, and excretion (ADME) properties (Hingorani et al. 2019; Van Norman 2019). Determining the first-in-human (FIH) dose, estimating systemic exposure, and characterizing dose–toxicity relationships all fundamentally depend on the accuracy of PK projections. Errors at this stage not only reduce the likelihood of clinical success but also pose a significant risk to patient safety.

The complexity of human PK prediction reflects fundamental species differences in physiology and drug disposition mechanisms that are not easily captured in preclinical models. Unlike laboratory animals, humans display distinct patterns of enzyme expression, transporter activity, and plasma protein binding, with considerable interindividual variability. Critical metabolic enzymes, such as cytochrome

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P450 isoforms, exhibit markedly different expression levels and catalytic activities across species, while genetic polymorphisms in these enzymes introduce additional layers of complexity unique to the human population (Evans and Relling 1999). Moreover, conventional *in vitro* systems fail to represent the dynamic, multi-organ interactions of human physiology, where factors such as blood flow, tissue distribution, and transporter–enzyme interplay operate under continuously changing conditions.

These fundamental challenges manifest differently across drug classes, creating class-specific complexities in prediction. Small molecules often face complications arising from extensive hepatic metabolism and genetic polymorphisms in metabolic enzymes, leading to substantial interindividual variability in drug exposure. Although target-mediated drug disposition may also occur with small molecules, it is particularly characteristic of biologics, resulting in nonlinear, dose-dependent clearance that varies according to target expression levels and binding kinetics (An 2020). For biologics, species-specific differences in neonatal Fc receptor (FcRn) recycling pathways and potential immunogenicity remain difficult to predict from preclinical studies (CaC et al. 2017).

To address these limitations, predictive approaches have evolved from primarily empirical extrapolation toward mechanism-informed and multimodal strategies. Traditionally, approaches such as allometric scaling, *in vitro*–*in vivo* extrapolation (IVIVE), and physiologically based pharmacokinetic (PBPK) modeling have been widely employed (Van Valkengoed et al. 2025). More recently, advancements such as artificial intelligence (AI)-driven machine learning (ML) algorithms and organ-on-a-chip (OoC) microphysiological systems have been integrated into predictive workflows, marking a transition toward more human-relevant and mechanistically grounded approaches (Wang et al. 2021; Obrezanova 2023).

Meanwhile, regulatory agencies are increasingly supporting the adoption of human-relevant prediction methods. Recent initiatives, such as the FDA's 2025 Roadmap for Reducing Animal Testing in Preclinical Safety Studies and parallel efforts by the European Medicines Agency (EMA), the Pharmaceuticals and Medical Devices Agency, and the Organisation for Economic Co-operation and Development (OECD), illustrate a global transition toward human-relevant approaches in drug development (FDA 2025). Although these initiatives primarily focus on safety assessment, this regulatory momentum is also driving the advancement of human PK prediction methods, positioning them beyond their traditional function as supplementary decision-support tools and establishing them as integral elements of modern drug development strategies.

This review examines advances in methodologies for human PK prediction—from conventional approaches to emerging technologies—by evaluating their predictive performance, advantages, and limitations through illustrative case studies. The review is organized to first discuss conventional approaches, including allometric scaling, IVIVE, and PBPK modeling, followed by an analysis of emerging methodologies such as AI and ML applications, as well as OoC technologies and their integration with computational frameworks. Figure 1 illustrates the evolution of human PK prediction approaches and highlights key milestones. Finally, current regulatory perspectives and future directions for implementing these methodologies in translational drug development are discussed. Ultimately, this review aims to evaluate the current state of human PK prediction methodologies and to identify opportunities for integrating complementary approaches into comprehensive translational drug development strategies.

Conventional prediction methods

An overview of conventional methods for human PK prediction is provided in Table 1, which summarizes their key features, advantages, limitations, and quantitative performance metrics derived from validation studies. The table facilitates direct comparison among conventional approaches and emerging AI/ML methods. Each approach is described in the subsequent subsections, followed by a comparative analysis in section “[Comparative analysis of conventional approaches](#)”.

Allometric scaling

Allometric scaling is among the earliest and most widely applied approaches in PK prediction. This empirical method leverages anatomical, physiological, and biochemical similarities among species to extrapolate pharmacokinetic parameters from animals to humans. Allometric scaling has become integral to drug development by enabling early estimation of human PK parameters when human data are unavailable or limited.

Basic principles

Physiological variables such as cardiac output, oxygen consumption, metabolic rate, and tissue perfusion do not scale linearly with body weight (BW) but instead follow nonlinear allometric relationships across species. In the 1880s, Max Rubner proposed that basal metabolic rate (BMR) increases proportionally with body surface area (BSA), where surface area corresponds to the square of length (L^2) and body mass

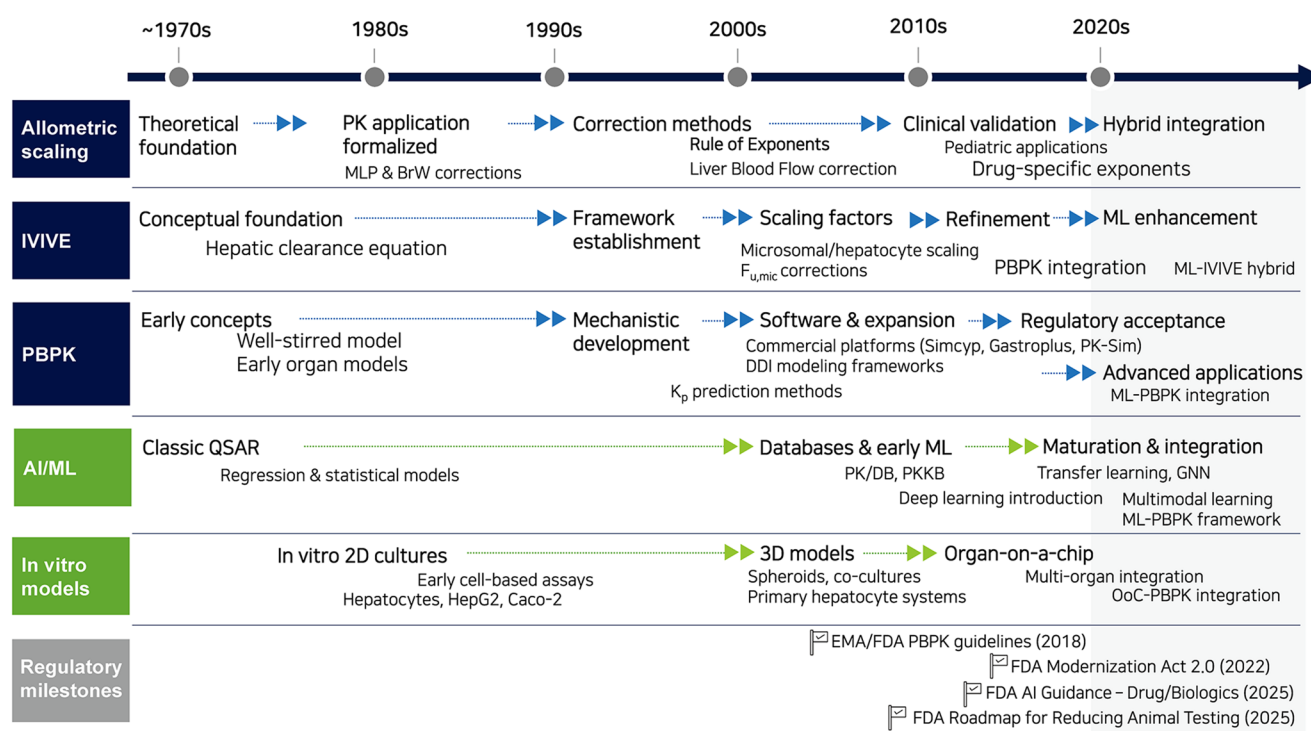


Fig. 1 Evolution of human pharmacokinetics prediction approaches. Historical timeline illustrating major PK prediction methodologies from the 1970s to the 2020s, encompassing traditional approaches

(allometric scaling, IVIVE, and PBPK), emerging technologies (AI/ML and organ-on-a-chip), and key regulatory milestones shaping the transition toward human-relevant prediction strategies

corresponds to volume (L^3). This *surface area hypothesis* predicted that BMR is proportional to $BW^{2/3}$, a relationship that remained widely accepted for decades (Boxenbaum 1982).

However, this assumption was later challenged when Max Kleiber's empirical studies on various mammalian species during the 1930s–1940s revealed a different scaling pattern, indicating that BMR is proportional to $\propto BW^{3/4}$ (Kleiber 1947). Subsequently, the West–Brown–Enquist model (West et al. 1997) provided a theoretical basis for this exponent by proposing that biological transport networks, such as vascular systems, adopt fractal branching structures to minimize energy expenditure and maximize transport efficiency. When expressed mathematically, these predictions correspond well with observed data and suggest that nonlinear scaling relationships arise from intrinsic constraints within biological network architecture (West et al. 1997).

In pharmacokinetics, these allometric principles are applied to predict clearance (CL), volume of distribution (V_d), and elimination half-life ($t_{1/2}$) from animal data to humans. Simple allometric scaling describes pharmacokinetic parameters (Y) as a power function of BW:

$$Y = a \cdot BW^b$$

where a is a species-independent scaling coefficient and b is the allometric exponent (Fig. 2). Empirically, the allometric exponent b is approximately 0.75 for CL, 1.0 for V_d , and 0.25 for both mean residence time (MRT) and $t_{1/2}$ (Boxenbaum 1982).

Evolution and advances

The simple body weight–based extrapolation has evolved to incorporate correction factors that address species-specific physiological differences. Boxenbaum introduced the maximum lifespan potential (MLP) and brain weight correction models, recognizing that longevity correlates inversely with hepatic cytochrome P450 metabolic activity (Boxenbaum 1982). These concepts were later formalized into the Rule of Exponents (ROE), which applies different correction schemes depending on the estimated allometric exponent values, while liver blood flow correction provides an alternative for flow-limited drugs (Mahmood 2002; Nagilla and Ward 2005). Implementation of these correction factors has demonstrated substantial predictive improvement, with the average fold error decreasing from 3.14 using simple allometry to 2.18 when applying ROE correction for hepatically eliminated compounds (Huh et al. 2011).

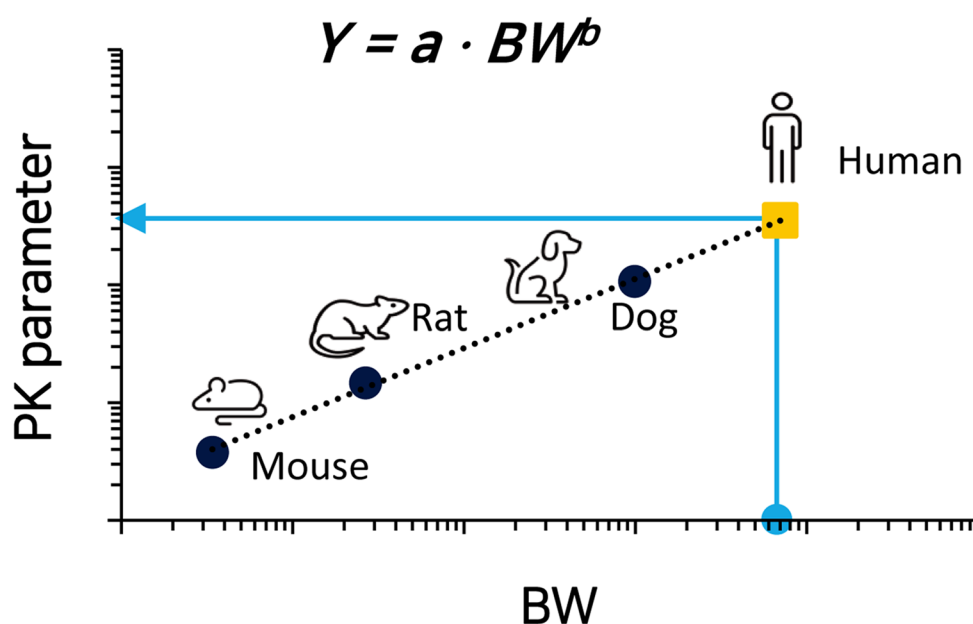
Contemporary frameworks have advanced beyond fixed theoretical exponents, as experimental evidence now

Table 1 Comparison of conventional and AI/ML-based PK prediction approaches

Method	Data requirements	Modeling complexity	Predictivity	Quantitative performance	Typical applications	Advantages	Limitations
Allo-metric scaling	• Animal PK parameters from ideally ≥ 3 species • Body weight • Optional correction factors (MLP, brain weight, liver blood flow)	• Low • Simple log-log regression	• Limited • Empirical, early approximation • Inconsistent across drug classes	• Simple allometry: AAFE 3.14 (Huh et al. 2011) • ROE-corrected: AAFE 2.18, 31% improvement (Huh et al. 2011) • Pediatric: Mostly within 2-fold; 20% within 25%, 34% within 50% (Liu et al. 2017) • mAbs: High accuracy with cynomolgus, $b=0.85$ (Deng et al. 2011)	• Early-stage human PK prediction • FIH dose selection • Interspecies scaling	• Very simple and fast • Minimal data needs • Useful in early drug development	• Assumes universal scaling exponents • Poor accuracy for protein-bound or low-clearance drugs • Cannot capture inter-individual variability
IVIVE	• In vitro clearance (HLM or hepatocytes), $f_{u,mic}$ • Scaling factors (MPPGL or HPGL, liver weight) • Human $f_{u,p}$, Q_H (and B/P) • Optional transporter data.	• Low to moderate • Simple framework • Accuracy depends on corrections and scaling	• Moderate • Often under-prediction, corrected by empirical factors	• Uncorrected: Systematic 4–5 fold underprediction (Hallifax et al. 2010) • Empirical scaling: Substantially improved (Tess et al. 2023) • ML-enhanced: 62% within 2-fold (external validation); AAFE 2.5 vs 2.8–3.3 traditional (Keefer et al. 2023)	• Prediction of hepatic clearance • Evaluation of metabolic liabilities • DDI risk assessment • Integration with PBPK	• Mechanistic basis • Extrapolation of enzyme/transporter effects • Extendable to nonlinear kinetics	• Sensitive to binding and scaling variability • Systematic under-/overprediction • Limited extrahepatic metabolism coverage
PBPK	• Physicochemical data ($\log P$, pK_a, solubility, permeability) • $f_{u,p}$, B/P, CL_{int} • System data: organ volumes, blood flows, etc.	• High • Large ODE-based models • Requires software and expertise	• Moderate to high • Broad applicability • Accepted by regulators	• Bottom-up predictions: 42.6% within 2-fold (oral, AAFE 2.8); 76.1% within 2-fold (i.v., AAFE 1.9) (Ahmad et al. 2020) • DDI (CYP3A4): 89% AUC, 93% C_{max} within 0.5–2 fold (Yang et al. 2025) • Oligonucleotides: 70–80% within 2-fold, >90% within 3-fold (avg fold error 1.5) (Derbalah et al. 2025)	• Extrapolation across species and populations • DDI prediction • Dose selection in special populations • Regulatory submissions	• Mechanistic • Predicts tissue concentrations • Broad applicability • Recognized by FDA/EMA	• Data-intensive • Parameter uncertainty and identifiability issues • Requires sensitivity analysis and validation
AI/ML	• Large training datasets (typically 500–5000+ compounds) • Molecular descriptors (ECFP, Mordred, RDKit) or SMILES • PK endpoint data (AUC, C_{max}, CL, V_d, etc.) • Optional: in vitro ADME data for hybrid approaches	• Moderate to high • Algorithm selection and tuning • Feature engineering required • Validation strategy critical	• Variable, highly endpoint-dependent • Strong for pattern recognition within training domain • External validation often shows degraded performance • Rapidly improving with advanced architectures	• CL: R^2 0.48–0.84, variable performance (Keefer et al. 2023; Jia et al. 2025) • AUC/C_{max}: R^2 0.61–0.93, endpoint-dependent (Li et al. 2024; Liu et al. 2024; Li et al. 2025) • Hybrid integrated: AAFE 1.84–2.33; GMFE 1.84 (Himstedt et al. 2024; Jia et al. 2025) • External validation gap: 30–50% R^2 reduction common (e.g., 0.63→0.32) (Miljkovic et al. 2021)	• Large-scale compound screening • ADME property prediction • Early drug discovery prioritization • Pattern recognition across chemical space • Integration with mechanistic models (hybrid approaches)	• High-throughput capability • Pattern detection in large datasets • Rapidly improving with new algorithms • No need for animal studies • Can identify non-obvious relationships	• Black-box nature (limited mechanistic insight) • External validation often shows degraded performance • Requires large, high-quality training datasets • Risk of overfitting and data leakage • Applicability domain limitations • Regulatory acceptance still emerging

IVIVE: in vitro-in vivo extrapolation; PBPK: physiologically based pharmacokinetics; AI/ML: artificial intelligence/machine learning; MLP: maximum lifespan potential; ROE: rule of exponents; HLM: human liver microsomes; $f_{u,mic}$: unbound fraction in microsomes; MPPGL: microsomal protein per gram liver; HPGL: hepatocytes per gram liver; $f_{u,p}$: unbound fraction in plasma; Q_H : hepatic blood flow; B/P: blood-to-plasma ratio; CL_{int} : intrinsic clearance; DDI: drug-drug interaction; FIH: first-in-human; mAbs: monoclonal antibodies; CYP3A4: cytochrome P450 3A4; AAFE: absolute average fold error; GMFE: geometric mean fold error; R^2 : coefficient of determination; AUC: area under the concentration-time curve; C_{max} : maximum plasma concentration; i.v.: intravenous; SMILES: simplified molecular input line entry system; ECFP: extended-connectivity fingerprints; ADME: absorption, distribution, metabolism, and excretion

Fig. 2 Prediction of a human PK parameter via a simple allometric scaling. The relationship $Y = a \cdot BW^b$ describes pharmacokinetic parameters (Y) as a function of body weight (BW), where a is the scaling coefficient, and b is the allometric exponent. Typical exponents are approximately 0.75 for clearance and 1.0 for volume of distribution (modified from (Kim et al. 2025))



indicates that allometric exponents are compound-dependent rather than universal constants (Mahmood 2018; Decker et al. 2024). Recent developments have also explored integrated methodologies combining allometric scaling with population pharmacokinetic modeling, showing promise for predicting concentration–time profiles in humans for both small molecules (Sharma et al. 2018; Kim et al. 2023) and therapeutic peptides (Kim et al. 2025).

Applications and case studies

Allometric scaling has been successfully applied to predict human pharmacokinetics not only for small molecules but also for therapeutic proteins and monoclonal antibodies (Mahmood 2009). For example, Deng et al. (2011) investigated allometric scaling for 13 therapeutic monoclonal antibodies (Deng et al. 2011). The study reported that scaling from cynomolgus monkey data alone, using a fixed allometric exponent of 0.85, produced the most accurate predictions of human clearance and concentration–time profiles. The superior predictive accuracy was attributed to the close physiological similarity between cynomolgus monkeys and humans, particularly their comparable FcRn-mediated recycling and antigen homology (Deng et al. 2011).

Allometric scaling has also been employed to predict the pharmacokinetics of drugs in special populations, such as pediatric patients, by extrapolating data from adults. Liu et al. (2017) systematically evaluated allometric scaling for pediatric dosing by analyzing 46 FDA-approved drugs with both adult and pediatric pharmacokinetic data (91 clearance predictions) (Liu et al. 2017). Simple $BW^{0.75}$ scaling predicted pediatric clearance values mostly within a twofold range of the observed data across administration

routes, elimination pathways, and age groups. Specifically, 18 drugs (20%) were predicted within 25% and 31 drugs (34%) within 50% of observed values, demonstrating unbiased predictive performance across all weight ranges. This study established that for children aged two years and older, allometric scaling represents a scientifically justified and regulatory-relevant approach for pediatric trial design and dose optimization (Liu et al. 2017).

Advantages and limitations

The principal advantages of allometric scaling include its rapid and straightforward implementation, minimal data requirements, and low modeling complexity. The method exhibits high predictive accuracy when metabolic pathways are conserved across species and can perform effectively with limited interspecies data, provided that appropriate correction factors are applied (Tang and Mayersohn 2011; Choi et al. 2019).

However, several inherent limitations arise from the assumption of universal scaling relationships. The fixed allometric exponent of 0.75 for clearance fails to account for compound-specific elimination mechanisms, leading to poor predictive accuracy for low-clearance drugs and highly protein-bound compounds (Huang and Riviere 2014). Species-dependent variations in plasma protein binding, transporter expression, and metabolic pathways are also inadequately represented by simple body weight–based relationships (Tang and Mayersohn 2011; Choi et al. 2019). Certain pharmacological classes require specialized scaling strategies: central nervous system drugs often benefit from brain weight–based scaling, whereas biologics exhibiting FcRn-mediated recycling necessitate more mechanistic

PBPK approaches (Sharma and McNeill 2009; Tang and Mayersohn 2011). Moreover, conventional allometric models cannot incorporate intra-species variability related to age, sex, or disease state (Van Valkengoed et al. 2025).

In vitro–in vivo extrapolation (IVIVE)

IVIVE predicts human PK parameters from in vitro metabolic or depletion rate data, providing a mechanistic framework that minimizes dependence on animal experimentation (Houston 1994). This methodology bridges experimental measurements and clinical pharmacokinetics through quantitative translation grounded in fundamental biological processes.

Basic principles

The conceptual foundation of IVIVE is derived from the hepatic clearance equation, $CL_H = Q \times ER$, first introduced by Rowland and Tozer in the 1970s. This principle was later formalized as the well-stirred model, which conceptualizes the liver as a single, homogeneously mixed compartment (Rowland et al. 1973). Subsequently, enzyme kinetic parameters ($CL_{int} = V_{max}/K_m$) were incorporated to directly link in vitro enzyme activity data with in vivo hepatic clearance, thereby establishing the mechanistic basis for quantitative extrapolation (Houston 1994).

To scale from in vitro systems to the human liver, IVIVE applies sequential multiplication by physiological scaling factors, such as microsomal protein per gram liver (MPPGL) and liver weight; enzyme abundance may also be used for isoform-specific scaling. Figure 3 illustrates the IVIVE workflow for predicting hepatic clearance (CL_H) from in vitro microsomal data. The final CL_H is typically calculated using the well-stirred model:

$$CL_H = \frac{Q_H \cdot f_B \cdot CL_{int}}{Q_H + f_B \cdot CL_{int}}$$



Fig. 3 Overall process of in vitro–in vivo extrapolation (IVIVE) to predict hepatic clearance (CL_H) using human liver microsomes. Intrinsic clearance (CL_{int} , in vitro) is first measured under linear conditions from microsomal incubations ($v/C \approx V_{max}/K_m$). Physiological scaling factors—microsomal protein per gram liver (MPPGL) and liver weight—

where Q_H is hepatic blood flow (blood basis), f_B is the unbound fraction in blood, and CL_{int} represents the scaled intrinsic clearance derived from microsomal or hepatocyte assays (Choi et al. 2019; Rowland and Pang 2022). The blood unbound fraction (f_B) is related to the plasma unbound fraction ($f_{u,p}$) through the blood-to-plasma ratio (B/P) according to the relationship $f_B = f_{u,p}/(B/P)$. When $B/P \approx 1$, $f_B \approx f_{u,p}$, and the equation simplifies accordingly. The well-stirred model assumes instantaneous mixing within the hepatic compartment, whereas alternative models—such as the parallel tube, distributed, and dispersion models—account for the structural heterogeneity of hepatic architecture (Rowland and Pang 2022).

Evolution and advances

Early empirical investigations by Houston established the foundational scaling framework, whereas systematic incorporation of correction factors emerged in the late 1990s with the introduction of unbound fractions in microsomes ($f_{u,mic}$) and plasma ($f_{u,p}$), along with the intersystem extrapolation factor (Obach 1999; Baker and Parton 2007). These refinements enabled quantitative scaling beyond intrinsic clearance estimation and marked the beginning of integration with PBPK modeling. More recent research has examined transporter–enzyme interplay and protein-binding-mediated uptake corrections for highly protein-bound compounds (Bowman et al. 2019; Francis et al. 2021), although these approaches remain under active evaluation.

Applications and case studies

Systematic validation studies have consistently identified underprediction as a major limitation of IVIVE and have established the use of empirical scaling factors as an effective corrective approach. Hallifax et al. (2010) reported that microsomal data underestimated clearance approximately fivefold, whereas hepatocyte data exhibited a fourfold underprediction; however, empirical scaling factors derived from observed–predicted correlations substantially

are then applied to obtain in vivo intrinsic clearance (CL_{int} , in vivo). Finally, hepatic clearance (CL_H) is predicted using models such as the well-stirred model (shown), parallel-tube model, or dispersion model, which incorporate hepatic blood flow (Q_H) and unbound blood fraction (f_B)

mitigated this bias (Hallifax et al. 2010). These findings were further corroborated by a comprehensive evaluation of 455 compounds, in which unified empirical scaling factors significantly improved prediction accuracy across diverse chemical classes, with microsomal and hepatocyte systems displaying complementary predictive performance (Tess et al. 2023).

Extending beyond empirical corrections, Keefer et al. (2023) explored the integration of ML approaches using data from 645 marketed drugs and 16 developmental compounds (Keefer et al. 2023). Their ML framework achieved an average absolute fold error (AAFE) of 2.5, outperforming conventional mechanistic models (AAFE 2.8–3.3) and identifying hepatocyte intrinsic clearance and fraction unbound as key determinants of predictive accuracy. These results highlight the potential of hybrid IVIVE–ML strategies, in which traditional IVIVE predictions are enhanced through ML algorithms trained on experimental clearance datasets, thereby improving robustness and generalizability of pharmacokinetic predictions.

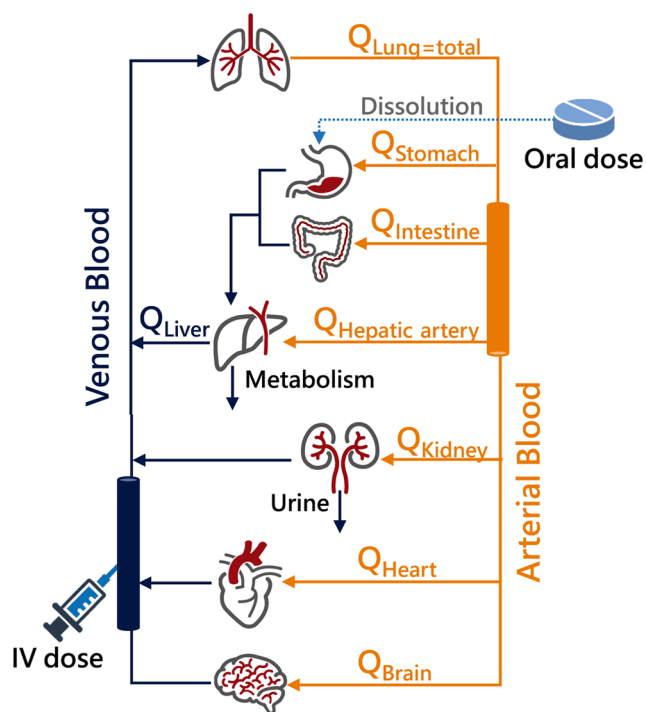


Fig. 4 Representative structure of a physiologically based pharmacokinetic (PBPK) model. Compartments represent anatomical organs connected by arterial and venous blood flow, where Q denotes organ-specific blood-flow rates. Drug administration routes are indicated: intravenous (IV) input to the venous compartment and oral input through dissolution in the gastrointestinal tract. Elimination pathways include hepatic metabolism and renal excretion (urine)

Advantages and limitations

IVIVE provides several important advantages, including mechanism-based prediction of pharmacokinetic behavior through quantification of protein binding and enzyme activity, as well as early identification of metabolic liabilities before animal studies. When integrated with PBPK models, IVIVE also facilitates the incorporation of hepatic physiology, enzyme expression, and transporter-mediated processes (Rowland et al. 2011; Jones and Rowland-Yeo 2013).

Despite these advantages, IVIVE exhibits several limitations that constrain its predictive accuracy. In vitro CL_{int} frequently overestimates or underestimates in vivo clearance because of scaling inaccuracies and incomplete representation of physiological conditions. The method additionally requires supplemental modeling to account for extrahepatic metabolism and transporter-mediated disposition. Furthermore, tissue-specific mechanisms and complex transporter–enzyme interactions remain difficult to capture accurately, thereby limiting the complete replacement of in vivo experimentation (Ito and Houston 2005; Chiba et al. 2009).

Physiologically based pharmacokinetic (PBPK) modeling

PBPK modeling provides a highly mechanistic framework for pharmacokinetic prediction by representing the human body as a system of interconnected organs, each characterized by defined tissue volumes, blood flow rates, and composition parameters. These models integrate drug-specific physicochemical properties with physiological determinants to simulate tissue concentration–time profiles and enable interspecies extrapolation through incorporation of species-dependent physiological differences.

Basic principles

PBPK models divide the body into anatomically distinct compartments representing major organs and tissues, each characterized by specific physiological volumes and blood flow rates derived from the literature. Each compartment is governed by a set of differential equations describing temporal changes in drug concentration, balancing input via arterial blood flow with output through venous drainage and local elimination processes (Gerlowski and Jain 1983; Jones and Rowland-Yeo 2013; Kim et al. 2018). A representative PBPK model structure is shown in Fig. 4. For non-eliminating tissues, the mass balance equation describing tissue concentration (C_T) is:

$$V_T \cdot \frac{dC_T}{dt} = Q_T \cdot C_A - Q_T \cdot C_{V,T}, C_{V,T} = \frac{C_T}{K_{p,T}}$$

where Q is the blood flow (L/h), C is the concentration (mg/L), and V is the tissue volume (L). The subscripts T, A, and V denote tissue, arterial, and venous compartments, respectively. $K_{p,T}$ is the tissue-to-plasma partition coefficient that determines the extent of drug distribution between blood and tissue. For eliminating tissues such as the liver, the equation includes an additional clearance term, typically under the well-stirred model assumption:

$$V_T \cdot \frac{dC_T}{dt} = Q_T \cdot C_A - Q_T \cdot C_{V,T} - CL_{int} \cdot f_{u,T} \cdot C_T$$

where CL_{int} represents the intrinsic clearance of the drug (L/h), and $f_{u,T}$ denotes the unbound fraction in the tissue.

PBPK models combine physiological parameters from the literature (e.g., organ volumes, blood flow rates) with experimentally derived drug-specific properties (e.g., intrinsic clearance and protein binding) to predict systemic and tissue-specific drug disposition. Tissue-to-plasma partition coefficients (K_p) may be obtained experimentally through tissue distribution studies or calculated using mechanistic prediction methods (Poulin and Theil 2002; Rodgers and Rowland 2006). The latter approach employs drug physicochemical characteristics—such as lipophilicity, pKa, and plasma protein binding—together with tissue composition data, and is widely used during early-stage drug development (Poulin and Theil 2002; Rodgers and Rowland 2006).

Evolution and advances

PBPK modeling has progressed from a theoretical framework to a practical tool in modern drug development, overcoming major technical barriers that initially limited its implementation. Early PBPK applications were constrained by mathematical complexity and extensive data requirements, particularly the reliance on large amounts of *in vivo* animal tissue concentration data (Rodgers and Rowland 2006). However, advances in K_p prediction methodologies and IVIVE enabled the use of hepatocyte and microsomal data, thereby reducing dependence on extensive tissue distribution studies. These developments have supported the establishment of more sophisticated PBPK structures, including permeability-limited models designed for compounds in which cellular membrane transport becomes the rate-limiting step.

Commercial software platforms such as Simcyp® (<http://www.certara.com/simcyp/>), GastroPlus® (<https://www.simulations-plus.com/>), and PK-Sim® (<https://www.open-systems-pharmacology.org/>), further democratized PBPK modeling through intuitive user interfaces and integrated physiological databases, effectively eliminating the need for extensive programming expertise (Jones and Rowland-Yeo

2013; Zhuang and Lu 2016). These tools now incorporate comprehensive physiological databases, automated parameter estimation algorithms, and virtual population libraries that enable non-programmers to construct and validate mechanistic PBPK models efficiently. The widespread availability of such platforms has transformed PBPK modeling from a specialized academic discipline into a routine component of pharmaceutical research and development.

Recent advancements are improving predictive performance through hybrid approaches that combine mechanistic modeling frameworks with clinical data optimization (Poggesi et al. 2014). In addition, emerging methodologies are integrating AI and ML algorithms for parameter estimation and refinement of prediction accuracy (Li et al. 2024). Regulatory authorities have increasingly endorsed PBPK modeling for drug–drug interaction (DDI) prediction and special population studies, reflecting growing confidence in its scientific validity while recognizing ongoing challenges that require continued methodological refinement.

Applications and case studies

PBPK modeling enables quantitative extrapolation across species, populations, administration routes, and dosing regimens, while simultaneously predicting tissue-specific concentrations and potential drug–drug interactions (Jones and Rowland-Yeo 2013; Abouir et al. 2021). PBPK modeling has gained substantial regulatory acceptance for predicting human pharmacokinetics, with approximately 30% of FDA-approved novel drugs incorporating PBPK approaches during their development (Sun et al. 2024). Major applications include the prediction of drug–drug interactions, organ impairment effects, pediatric pharmacokinetics, and drug–gene interactions, with many PBPK-based models now formally recognized by the FDA as supportive evidence in regulatory submissions (Sun et al. 2024).

A recent PBPK study addressed the persistent challenge of predicting CYP3A4 induction-mediated drug–drug interactions using rifampicin as a prototypical inducer (Yang et al. 2025). A whole-body PBPK model was developed and verified against clinical pharmacokinetic data, achieving predictions for C_{max} , AUC, and CL values within $\pm 25\%$ of observed outcomes—meeting conventional bioequivalence acceptance criteria. When applied to a panel of 28 FDA-approved small molecules, the model demonstrated high predictive accuracy: approximately 89% of AUC ratios and 93% of C_{max} ratios fell within the conventional 0.5- to 2-fold acceptance range, while about 79% of AUCR predictions met the same criterion. In contrast, static prediction methods achieved only about 14% compliance under identical evaluation conditions. These results underscore that PBPK modeling provides a quantitatively robust framework for

evaluating enzyme induction liabilities, thereby enhancing risk assessment and optimizing clinical trial design in early drug development.

More recent research has expanded PBPK modeling to encompass novel therapeutic modalities, including oligonucleotide-based therapeutics. A whole-body PBPK model was recently developed for both N-acetylgalactosamine-conjugated and unconjugated antisense oligonucleotides (Derbalah et al. 2025). The model incorporated drug distribution into key tissues—such as the liver, kidney, and spleen—along with cellular uptake and nonspecific absorption pathways, thereby accounting for the complex disposition characteristics of these large, charged molecules. Evaluation against preclinical and clinical pharmacokinetic datasets demonstrated that approximately 70–80% of AUC and $C_{\max}$ predictions were within a twofold range of observed values, and over 90% within a threefold range, with an average fold error of about 1.5. These findings underscore the growing utility of PBPK modeling in supporting translational development and quantitative prediction for oligonucleotide therapeutics.

Advantages and limitations

PBPK modeling enables quantitative extrapolation across species, populations, administration routes, and dosing regimens, thereby facilitating the translation of pharmacokinetic findings from preclinical studies to clinical settings. Prediction of tissue concentrations is particularly valuable for elucidating target-site exposure and assessing potential toxicities. In addition, PBPK models are highly effective in predicting drug–drug interactions through mechanistic integration of enzyme- and transporter-mediated kinetics (Sun et al. 2024; Yang et al. 2025). Regulatory authorities increasingly recognize PBPK modeling as robust supporting evidence for dose selection, special population assessments, and regulatory submissions, with both FDA and EMA advocating its use in official guidance documents (EMA 2018; Abouir et al. 2021).

However, bottom-up PBPK predictions demonstrate variable accuracy across administration routes—achieving approximately 42.6% of predictions within a twofold error range for oral dosing, compared with 76.1% for intravenous administration (Ahmad et al. 2020)—highlighting the persistent challenges in modeling oral absorption. The approach requires numerous high-quality physiological and drug-specific parameters and is often constrained by issues of parameter identifiability and redundancy. Furthermore, PBPK models exhibit limited capacity to capture interindividual variability without extensive sensitivity or population-based analyses (Jones et al. 2015; Peters and Dolgos 2019). These limitations underscore the continuing need for

hybrid modeling strategies that integrate mechanistic frameworks with clinical data to enhance predictive reliability and translational applicability.

Comparative analysis of conventional approaches

Conventional pharmacokinetic prediction methods differ fundamentally in their data requirements, modeling complexity, and predictive performance (Table 1). Allometric scaling requires minimal input parameters, such as body weight and basic PK data, and involves relatively simple calculations. In contrast, IVIVE relies on in vitro metabolic data and entails moderate computational effort, whereas PBPK modeling demands extensive physiological and drug-specific parameters, together with sophisticated modeling frameworks. These varying resource requirements determine practical applicability and influence method selection throughout the drug development continuum.

Despite differences in computational complexity, improvements in predictive performance follow consistent trends across all methods. Methodological refinement typically yields a 20–40% enhancement in accuracy—achieved through correction factors in allometric scaling, empirical scaling adjustments in IVIVE, or specialized parameterization in PBPK models. However, all approaches predict intravenous pharmacokinetics substantially more accurately than oral pharmacokinetics (e.g., 76.1% vs 42.6% within twofold for PBPK), highlighting absorption modeling as a common limitation regardless of model complexity.

Beyond these shared trends, application-specific predictive performance varies considerably. PBPK modeling achieves 70–93% accuracy in well-characterized systems, such as DDIs and oligonucleotide therapeutics, but only about 42.6% accuracy for general oral predictions. Allometric scaling demonstrates moderate precision (AAFE 2.18) while maintaining a low data burden, whereas IVIVE occupies an intermediate position in both performance and data requirements. These characteristics suggest distinct optimal use cases: allometric scaling when minimal preclinical data are available; IVIVE for evaluating hepatic clearance; and PBPK modeling when extensive parameterization is justified by mechanistic or regulatory objectives.

Emerging approaches in human PK prediction

Artificial intelligence and machine learning–based methods

AI–based and ML–driven approaches for predicting human PK represent a paradigm shift from traditional modeling

frameworks. Whereas conventional methods emphasize mechanistic understanding and parameter estimation derived from experimental data, AI- and ML-based approaches directly predict key PK parameters—including CL, V_d , $t_{1/2}$, AUC, and C_{max} —from molecular descriptors and in vitro ADME characteristics (Obrezanova et al. 2022). The rapid expansion of these data-driven methods has been facilitated by the availability of large-scale human PK databases and continual advances in machine learning algorithms, thereby creating new opportunities to enhance efficiency and accelerate drug development pipelines.

Basic principles

ML methods employ supervised learning algorithms to establish quantitative relationships between molecular features and PK outcomes, thereby enabling the direct prediction of human PK parameters without relying on explicit mechanistic assumptions (McComb et al. 2022; Poweleit et al. 2023; Ahmadi et al. 2024).

Feature representation defines how molecular information is encoded for model input. Common encoding strategies include the use of calculated molecular descriptors, chemical fingerprints—such as extended-connectivity fingerprints (ECFP)—and graph-based molecular representations in which atoms are treated as nodes and chemical bonds as edges (Jiang et al. 2021). In vitro ADME properties can also be integrated as supplementary input features. Feature selection algorithms are then applied to identify the most informative descriptors while minimizing the risk of model overfitting.

Model development involves systematic data preprocessing steps, including management of missing values, detection of outliers, and normalization of input features. Rigorous validation strategies are essential to evaluate model generalizability: k-fold cross-validation provides internal performance estimates, whereas external validation using temporally or structurally distinct datasets assesses real-world applicability. To prevent data leakage—where information from the test set inadvertently influences the training phase—appropriate dataset partitioning strategies must be implemented. External validation typically demonstrates lower predictive performance than internal validation; for instance, Miljkovic et al. reported that the coefficient of determination (R^2) decreased from 0.63 to 0.32, underscoring the importance of evaluating models against independent datasets (Miljkovic et al. 2021).

Evolution and advances

ML model development relies fundamentally on both the quality of training data and the methodological rigor of

model construction. Curated datasets—such as the compilation by Lombardo et al., which includes 1352 experimentally determined human PK parameters—have provided standardized resources for model benchmarking and validation (Lombardo et al. 2018). In addition, specialized repositories such as PK/DB, PKKB, and PK-DB supply data optimized for computational modeling applications (Moda et al. 2008; Cao et al. 2012; Grzegorzewski et al. 2021; Danishuddin et al. 2022). Representative examples of these databases are summarized in Table 2. Web-based prediction platforms—including ADMETlab, pkCSM, and related tools—have made AI-based pharmacokinetic modeling broadly accessible, integrating ensemble learning architectures and gradient-boosting regression frameworks trained on curated PK datasets (Pires et al. 2015; Dong et al. 2018; Fu et al. 2024; Niu et al. 2024). More recently, graph neural networks have enabled the direct learning of molecular representations from chemical structure topology, providing an end-to-end approach for PK property prediction (Fralish et al. 2023).

ML algorithms applied to PK prediction span a broad spectrum—from traditional approaches such as random forests, support vector machines, and gradient-boosting models to advanced deep learning architectures, including artificial neural networks and graph convolutional networks (Ahmadi et al. 2024). Deep learning approaches have demonstrated superior performance in modeling complex, non-linear molecular relationships (Niu et al. 2024), whereas graph neural networks represent chemical structures as graphs, enabling simultaneous capture of both local and global molecular features (Jiang et al. 2021). In addition, transfer learning and multi-task learning strategies address data scarcity by leveraging preclinical or animal datasets to improve model generalization and predictive robustness (Altae-Tran et al. 2017; Zakharov et al. 2019).

Uncertainty quantification and model explainability have emerged as critical research areas. Ensemble-based methods and Bayesian inference frameworks provide probabilistic confidence estimates for individual predictions (Hirschfeld et al. 2020). Explainable AI techniques—such as attention mechanisms and feature attribution algorithms—identify the molecular substructures most influential in model predictions (Holzinger et al. 2019; Jiménez-Luna et al. 2020). Collectively, these advances enhance model transparency, interpretability, and trustworthiness, thereby supporting broader regulatory acceptance.

Applications and case studies

AI-based approaches for human PK prediction have expanded rapidly across diverse therapeutic areas and modeling objectives. A structured literature search conducted across PubMed, Scopus, and Web of Science (1990–2025)

Table 2 Publicly available databases providing pharmacokinetic data

Name	Number of compounds/scope	Data	Description	Website	Reference
PK/DB (2008)	1,203 compounds; 2973 PK measurements (2008 article)	• HIA, F, PPB, BBB • Solubility • in silico ADME models • PK indices	• Published in 2008 as a PK/ADME resource • Original website no longer accessible, dataset details available only from the article	Unavailable	(Moda et al. 2008)
PKKB (Pharmacokinetics Knowledge Base)	1,685 drugs; $\geq 10,000$ ADME/T measurements (2012 article)	• logP, solubility, pKa, HIA, Caco-2 • F, PPB, B/P ratio • V_d, $t_{1/2}$, CL, excretion	• Large-scale ADME/T/PK database built by Soochow Univ. • Currently reported as inaccessible in Database Commons	Unavailable	(Cao et al. 2012)
e-Drug3D	2,162 structures; 1712 NMEs; PK parameters (V_d , CL, $t_{1/2}$, PPB, F, C_{max}/T_{max}) (accessed 2025–08)	• 3D structures (SDF), human PK parameters (FDA labels) • PD (targets) • FDA NDA label links	• Database integrating chemical structures with PK/PD and regulatory data • Updated annually	https://chemoinfo.ipmc.cnrs.fr/MOLDB/index.php	(Pihan et al. 2012)
ChEMBL	2,878,135 compounds; 21,123,501 activities; 16,003 targets (as of 2025–07–28)	• Bioactivity • ADME assays (e.g., $t_{1/2}$, F) • target/interaction data	• Maintained by EMBL-EBI • One of the largest open bioactivity resources • Includes ADME/PK assay metadata	https://www.ebi.ac.uk/chembl	(Zdravil 2025)
PK-DB (2021, König group)	512 studies; 1457 groups; 6308 individuals; 3148 time-courses; 73,017 outputs (2021 article)	• C-t curves • PK parameters (CL, AUC, $t_{1/2}$) • Subject characteristics • Interventions • REST API	• Open PK database for clinical and translational research • Provides standardized units, error/variance, metadata, and full API	https://pk-db.com	(Grzegorzewski et al. 2021)
DrugBank	18,494 drug entries (3,006 approved small-molecules, 1757 biologics; v5.1.13, released 2025–01–02)	• PK summaries ($t_{1/2}$, CL, F, PPB) • MOA, targets, interactions	• Widely used drug knowledge base • Free academic license allows partial data download	https://go.drugbank.com	N/A
PubChem	119M compounds; 322M substances; 295M bioactivities (as of 2024–09–12, 2025 NAR update)	• Chemical entities • Bioassays • Annotations • ADME-related metadata	• NIH/NCBI open chemical database • ADME/PK direct values limited, but annotations and assay coverage are extensive	https://pubchem.ncbi.nlm.nih.gov	N/A

PK: Pharmacokinetics; ADME/T: Absorption, Distribution, Metabolism, Excretion, and Toxicity; HIA: Human Intestinal Absorption; F: Bioavailability; PPB: Plasma Protein Binding; BBB: Blood-Brain Barrier; CL: Clearance; V_{ss} : Steady-State Volume of Distribution; $t_{1/2}$: Half-life; C_{max} : Maximum Plasma Concentration; T_{max} : Time to Reach Maximum Plasma Concentration; V_d : Volume of Distribution; CL_{int} : Intrinsic Clearance; fu: unbound fraction in plasma; B/P ratio: Blood-to-Plasma Ratio; DDI: Drug-Drug Interaction; PD: Pharmacodynamics; MoA: Mechanism of Action; NIH: National Institutes of Health; NCBI: National Center for Biotechnology Information

identified 1617 unique studies applying AI and ML methodologies to human PK prediction. Representative examples are summarized in Table 3, with cross-method performance comparisons provided in Table 1.

Multimodal learning frameworks developed by Iwata et al. predict human total CL and V_d directly from molecular structures (Iwata et al. 2021). These ML-derived parameters substitute experimentally measured values as direct inputs to PBPK model compartments, thereby enabling PK simulations without prior in vitro studies and improving the accuracy of preclinical-to-clinical translation relative to traditional IVIVE methods. Li et al. subsequently demonstrated reduced PBPK models in which ML-derived molecular descriptors serve as computational surrogates for

experimental measurements, achieving improved accuracy in quantitative PK predictions (Li et al. 2024).

DeepCt neural networks enable direct prediction of plasma concentration–time profiles from molecular structural features alone. This method reconstructs concentration–time curves following both single- and multiple-dose administrations (Beckers et al. 2024). DeepCt achieved a coefficient of determination (R^2) of approximately 0.66 for intravenous administration, with an average fold error of roughly twofold. However, the model generally requires large training datasets and remains limited in extrapolation to novel chemical scaffolds (Beckers et al. 2024).

Recent studies have demonstrated hybrid integration strategies that combine ML-based parameter estimation with

Table 3 Case examples of AI-based prediction of the pharmacokinetics in humans

Reference	N	Predict target	Descriptor types (Inputs)	Modeling method	Performance
(Ye et al. 2019)	1104 FDA drugs	f, PPBR, V_{ss} , $t_{1/2}$	ECFP (1024 bits), physchem	Transfer learning, multi-task DNN (DeepPharm)	acc=63.3% (V_{dss}); acc=66.7% ($t_{1/2}$)
(Miljkovic et al. 2021)	1001 drug-dose pairs	12 PK parameters (AUC, F, C_{max} , CL, $t_{1/2}$, T_{max} , V_{ss} , V_d/F)	SMILES, 2D descriptors	RF, XGBoost	$R^2=0.63$ (AUCPR), $R^2=0.68$ ($C_{max, PO}$); $R^2=0.32$ (External AUCPR)
(Jang et al. 2022)	3,627 PK-DDI pairs	DDI fold-change (AUC, C_{max})	FDA drug labels, DrugBank features	Bagged regression trees	Internal RMSE=0.596; External $R^2=0.769$
(Keefer et al. 2023)	1352 drugs (IV PK, ADME)	CL_{int} , CL_p	In vitro ADME (Clint, fu, logD)	Mechanistic IVIVE, ML IVIVE (XGBoost), QSAR	External 16 drugs: $R^2=0.84$, 62% ≤ 2 -fold
(Wu et al. 2024)	TDC ADME datasets ($n=4637-98$)	$f_{u,p}$, V_{ss} , CL_{app} , BPR, papp, K_i	SMILES, RDKit descriptors	GNN, RF, PopPK hybrid	Revaprazan $R=0.84-0.89$; Vonoprazan pred 88.9% vs obs. 76.4%
(Liu et al. 2024)	25k simulated profiles	C_{max} , AUC, $t_{1/2}$	Time-conc. profiles	Deep learning framework (Deep-NCA, sequence-to-scalar model)	$R^2=0.85$ ($C_{max}/dose$), $R^2=0.93$ (T_{max})
(Li et al. 2024)	$f_{u,p}=2292$; Caco-2=6083; $CL_t=1215$	$f_{u,p}$, Caco-2, CL_t , AUC, C_{max} , V_{ss}	Mordred, MW, pKa	SVR, RF, XGB, GBM, D-MPNN; inputs to PBPK	AAFE=2.8 ($t_{1/2}$); AAFE=2.00 (AUC_{inf}); AAFE=2.00 (CL); AAFE=2.12 (V_{ss})
(Li et al. 2025)	5187 profiles (~120 drugs)	AUC, C_{max} , T_{max} , $t_{1/2}$, CL/F, V_z/F , MRT, F	SMILES, CNN, physicochem	Multimodal DL (MMPK)	Test $R^2=0.61-0.72$ (AUC, C_{max} , CL/F, V_z/F , $t_{1/2}$)
(Himstedt et al. 2024)	40 orally administered NCEs (phase 1 PK)	CL/F, V_{ss}/F , C_{max} , C_{24h} , MRT_{tot} , $t_{1/2}$, full C-t curves	In vitro ADME, multi-species PK, physchem	Mechanism-based integration (allometry, IVIVC, hepatocyte scaling, MRC)	AAFE=2.04 (CL/F); AAFE=1.97 (V_{ss}/F); AAFE=2.33 (C_{max}); GMFE=1.84 (C-t curve)
(Jia et al. 2025)	773 IV C-t curves (>4-6k $F_u/CL/V_{ss}/pKa$)	Human IV C-t curve, F_u , CL, V_{ss} , pKa	SMILES, Mordred, RDKit, MACCS, FCFP6; logP, MW, pKa, infusion type	QSAR (RF, SVM, XGB, Consensus) PBPK hybrid, Hierarchical ML (RF, XGB)	$R^2=0.69$ (F_u); $R^2=0.48$ (CL); $R^2=0.60$ (V_{ss}); $R^2=0.94$ (pKa acidic); GMFE=1.84 (C-t curve)
(Iwata et al. 2025)	10k virtual subjects; ext. 64 pts	Human plasma C-t (remifentanyl)	Age, lean body mass, infusion rate, C_p (T_{infcat})	8 ML models (RF, GB, XGB, kNN, SVM, NN, Ridge, LASSO). Best=RF/GB	Virtual: RF $R^2 \approx 0.99$ (MSE=0.01); Real-world: RF $R^2=0.961$ (RMSE=0.045)

PK: Pharmacokinetics; ADME: Absorption, Distribution, Metabolism, and Excretion; FDA: Food and Drug Administration; PPBR: Plasma Protein Binding Ratio; V_{ss} : Steady-State Volume of Distribution; $t_{1/2}$: Half-life; ECFP: Extended-Connectivity Fingerprints; physchem: Physicochemical properties; DNN: Deep Neural Network; RF: Random Forest; XGBoost: Extreme Gradient Boosting; AUCPR: Area Under the Precision-Recall Curve; C_{max} : Maximum Plasma Concentration; RMSE: Root Mean Squared Error; CL_{int} : Intrinsic Clearance; f_u : Unbound fraction in plasma; logD: Logarithm of Distribution Coefficient; IVIVE: In Vitro to In Vivo Extrapolation; QSAR: Quantitative Structure-Activity Relationship; BPR: Blood-to-Plasma Ratio; K_i : Inhibition Constant; SMILES: Simplified Molecular Input Line Entry System; RDKit: Open-source Cheminformatics Toolkit; GNN: Graph Neural Network; PopPK: Population Pharmacokinetics; Deep-NCA: Deep Learning-based Noncompartmental Analysis; T_{max} : Time to Maximum Concentration; Mordred: Molecular descriptor toolkit; MW: Molecular Weight; pKa: Acid dissociation constant; GBM: Gradient Boosting Machine; D-MPNN: Directed Message Passing Neural Network; PBPK: Physiologically Based Pharmacokinetics; CNN: Convolutional Neural Network; V_z/F : Apparent Terminal Volume of Distribution; MRT: Mean Residence Time; F: Bioavailability; NCE: New Chemical Entity; physchem: Physicochemical properties; MMPK: Multimodal Pharmacokinetic Prediction; AAFE: Absolute Average Fold Error; GMFE: Geometric Mean Fold Error; $C_p(T_{infcat})$: Plasma concentration at termination of infusion; kNN: k-Nearest Neighbors; Ridge: Ridge Regression; LASSO: Least Absolute Shrinkage and Selection Operator

mechanistic PBPK modeling in sequential or iterative workflows. Neural networks trained on PBPK-simulated datasets have accurately reproduced AUC and C_{max} values, thereby accelerating compound screening and early-stage model refinement (Gruber et al. 2024). More recently, a hybrid modeling framework that integrates ML-based parameter inference with mechanistic PBPK modeling has been introduced (Jia et al. 2025). In this approach, ML models

predict molecular property descriptors—such as partition coefficient (logP), aqueous solubility, and clearance-related features—which are then used to populate PBPK input parameters, substituting traditional experimentally measured values. The underlying PBPK model structure and physiological constraints are retained, with the mechanistic component serving as the simulation engine for plasma concentration–time profile generation.

Advantages and limitations

AI-based approaches for human PK prediction offer several distinct advantages over traditional methodologies, particularly in computational efficiency and predictive accuracy. ML models enable direct prediction of PK parameters from molecular structures early in the drug discovery process, thereby eliminating extensive experimental testing and accelerating compound screening (Obrezanova 2023). AI algorithms can process high-dimensional, multimodal datasets and integrate diverse sources of information, including chemical structures, physicochemical descriptors, and in vitro ADME data (Iwata et al. 2021; Li et al. 2025). Advanced ML algorithms have demonstrated superior predictive performance in comparative studies, often outperforming conventional pharmacokinetic modeling and IVIVE approaches (Woillard et al. 2021). AI-driven models are also cost-efficient, reducing dependence on animal experiments and enabling high-throughput predictions across extensive compound libraries to support virtual screening and compound prioritization. However, these advantages have been observed primarily under controlled benchmarking conditions and may not directly translate to regulatory-grade decision-making without additional model validation, interpretability assessments, and standardization safeguards.

The primary limitation of AI-based PK prediction lies in the scarcity of large, high-quality human PK datasets, which typically include only 1400–2000 compounds—far fewer than the tens of thousands available for animal studies (Lombardo et al. 2018). This data scarcity is further compounded by an inherent bias toward compounds with favorable PK characteristics that have successfully advanced through clinical development, resulting in gaps in chemical space coverage and restricted model generalizability (Poweleit et al. 2023). Although substantial progress has been achieved in model explainability techniques, many advanced ML models—particularly deep learning architectures—continue to function as “black boxes,” thereby limiting mechanistic interpretability and regulatory acceptance (McComb et al. 2022). Unlike mechanistic models that permit explicit parameter exploration, ML-based approaches cannot simulate alternative dosing scenarios or perform “what-if” analyses, which constrains their applicability in dose optimization and clinical decision-making. Furthermore, ML models are prone to extrapolation errors when applied to novel chemical scaffolds or human populations that were not represented in the training data. Despite advances in uncertainty quantification, practical implementation of these methods remains limited, making it difficult to assess prediction reliability for novel compounds. Additional challenges include variability in dataset quality and

model performance degradation when models are deployed on input data that deviate from the training domain, underscoring the need for continuous model maintenance, recalibration, and validation (FDA 2025).

Advanced in vitro models: Organ-on-a-Chip

Advanced in vitro models encompass three-dimensional (3D) culture systems, perfusion-based platforms, and engineered tissue constructs that more accurately recapitulate human physiological conditions than conventional two-dimensional (2D) cell cultures. Among the various emerging systems—such as spheroids, organoids, and bio-reactor-based cultures—this review focuses primarily on OoC technology as a representative example of contemporary in vitro modeling approaches. OoC systems are particularly relevant to human PK prediction and are increasingly recognized by regulatory agencies as integral components of new approach methodologies (NAMs) frameworks.

Basic principles

OoC platforms integrate human-derived cells within engineered microfluidic devices to reproduce essential aspects of tissue or organ physiology in vitro (Huh et al. 2010). These microscale systems manipulate extremely small fluid volumes while allowing precise control over the local cellular microenvironment (Whitesides 2006). Recent advances have linked quantitative outputs from OoC systems with PBPK modeling and ML-based computational methods, establishing an integrated framework that enhances IVIVE and improves the prediction of human pharmacokinetics (Tsamandouras et al. 2017).

At the microscale (10^{-9} – 10^{-18} L), fluid flow remains laminar, and molecular transport occurs primarily through diffusion (Whitesides 2006). This allows the creation of stable gradients of nutrients, oxygen, and signaling molecules within microchannels. Controlled perfusion generates physiologically relevant shear stress, enabling endothelial and epithelial cells to develop barrier integrity and polarized transport activity (Bhatia and Ingber 2014). Mechanical cues—such as cyclic stretching that mimics breathing in lung models and peristaltic-like motions in gut chips—promote cellular differentiation and enhance transporter function (Huh et al. 2010). Collectively, these biophysical mechanisms create a microenvironment that enables OoC systems to recapitulate in vivo-like physiological responses more accurately than static cell culture models.

Evolution and advances

The evolution from basic microfluidic systems to OoC platforms was driven by the incorporation of living human cells into engineered microchannels subjected to dynamic mechanical stimuli. The lung-on-a-chip model successfully recreated the alveolar–capillary interface under cyclic strain, reproducing breathing-associated mechanical motion and strain-dependent toxicological responses (Huh et al. 2010). Similarly, intestine-on-a-chip systems incorporated continuous perfusion and peristaltic-like mechanical motions, promoting epithelial polarization and enabling long-term co-culture with commensal microbiota (Kim et al. 2012).

Subsequent development led to multi-organ microphysiological circuits designed to model ADME processes within interconnected microfluidic loops. Gut–liver co-culture platforms demonstrated that both permeability and metabolic clearance could be quantified under continuous perfusion for compounds such as diclofenac and hydrocortisone (Tsamandouras et al. 2017). More advanced systems integrating four to ten tissues introduced central mixing chambers and pneumatic micropumps, sustaining phenotypic stability for several weeks and enabling reproducible PK assessments (Edington et al. 2018).

Modern OoC platforms now generate quantitative PK parameters directly applicable to translational pharmacology. Intestinal chips yield apparent permeability (P_{app}) values that can be converted into effective permeability and absorption rate constants; liver chips provide intrinsic clearance estimates scalable to hepatic clearance; and multi-organ assemblies produce systemic parameters—such as AUC, C_{max} , and T_{max} —that can be integrated into PBPK modeling frameworks (Herland et al. 2020).

Applications and case studies

A vascularized multi-organ OoC network provided quantitative evidence that chip-derived data can reliably predict human PK responses (Herland et al. 2020). In a gut–liver–kidney–vascular configuration, systemic nicotine exposure values deviated by less than 15% from clinically observed data. Following administration of 4.2 mg nicotine via chewing gum, the predicted C_{max} values ($0.050\text{--}0.054\text{ }\mu\text{M}$) closely matched the clinical mean ($0.052 \pm 0.009\text{ }\mu\text{M}$), with AUC deviations ranging from approximately 9% to 23%. For intravenous cisplatin, the platform accurately reproduced patient concentration–time profiles (Lin's concordance correlation coefficient, $\rho \approx 0.98$) while also capturing relevant pharmacodynamic endpoints, including bone marrow cytopenias and renal transporter modulation.

An *in silico* framework has also been developed to employ gut–liver OoC systems as experimental sources of

PBPK–relevant parameters rather than as standalone predictive models (Milani et al. 2024). In this hybrid framework, chip-generated concentration–time data are fitted using compartmental ODEs to estimate absorption rate constants and intrinsic clearance, which are subsequently incorporated as fixed-parameter inputs within PBPK models while maintaining the mechanistic model structure. This approach further proposes experimental design strategies wherein chip geometry, flow rates, and ADME properties are computationally modeled in advance to optimize parameter identifiability and reduce redundant empirical assays.

Advantages and limitations

OoC platforms provide several significant advantages for human PK prediction. These systems recreate physiologically relevant microenvironments featuring controlled shear stress and mechanical stimuli, thereby more accurately reproducing *in vivo* conditions than conventional static cultures. Their multi-organ integration capabilities allow sequential representation of ADME processes, while real-time monitoring facilitates dynamic evaluation of drug transport, metabolism, and interactions. Furthermore, integration of OoC data with PBPK modeling generates experimentally grounded permeability, clearance, and transporter kinetic parameters that enhance IVIVE and improve systemic PK prediction accuracy (Tsamandouras et al. 2017; Yang et al. 2022).

Despite these advantages, several limitations hinder large-scale implementation. Most OoC studies remain confined to a limited number of representative compounds and are constrained by low experimental throughput—current devices typically contain only a few dozen microchambers per platform (Garreta et al. 2021). Technical challenges include non-specific adsorption of lipophilic compounds to device materials (e.g., polydimethylsiloxane, PDMS), pressure differentials across parallel channels, and operational complexity (Beebe et al. 2002; Huh et al. 2010). The technology also requires specialized expertise for device fabrication, fluidic control, and system calibration, while limited inter-laboratory reproducibility undermines cross-study comparability. High fabrication costs, labor-intensive operation, and challenges in scaling further restrict accessibility. These sources of experimental variability directly affect concentration–time profiles, parameter identifiability, and quantitative extrapolation accuracy, particularly when adsorption and flow-dependent transport are not explicitly characterized.

Consequently, OoC-derived results are more appropriately interpreted as parameter-informing or hypothesis-generating data rather than definitive predictors of human PK. Although OoC systems are increasingly recognized within

regulatory science frameworks (e.g., FDA NAMs initiatives; OECD AOP/NAM frameworks), no formal regulatory guideline or validated testing standard has yet been established due to persistent challenges related to standardization, reproducibility, throughput, and material-dependent artifacts.

Current challenges and future perspectives

Methodological challenges

Beyond the technology-specific limitations outlined in previous sections, emerging methodologies share several overarching challenges when translated into regulatory or decision-making contexts. While traditional approaches have undergone decades of refinement within well-established validation frameworks, AI-based and advanced in vitro systems continue to face structural and methodological gaps that require further development.

Extrapolation risk is particularly critical for data-driven approaches. AI models trained on existing compound libraries often exhibit limited generalizability when applied to novel chemical scaffolds, untested dosing regimens, or population groups underrepresented in the training datasets. Similarly, OoC systems validated using small compound panels demonstrate considerable uncertainty when predicting pharmacokinetic or pharmacodynamic responses for structurally diverse molecules or when scaling results from microphysiological environments to whole-organ or systemic levels.

Uncertainty quantification remains insufficiently developed across these emerging methodologies. PBPK models benefit from established sensitivity and uncertainty analysis frameworks, whereas AI models frequently provide only point estimates without associated confidence intervals. OoC-derived parameters similarly lack standardized measures of experimental variability. This discrepancy between apparent precision and actual reliability becomes particularly consequential when model-derived predictions inform safety-critical or regulatory decision-making.

Cross-method integration introduces further obstacles stemming from incompatible data formats, inconsistent metadata structures, and divergent validation standards. The lack of harmonized experimental protocols and context-specific performance benchmarks hampers meaningful comparison among methodologies and constrains the development of integrated predictive workflows. Overcoming these challenges will require not only continued technical refinement but also coordinated consensus-building regarding how emerging PK prediction methods should be

validated, interpreted, and standardized within translational and regulatory frameworks.

Regulatory challenges

The methodological limitations described above have direct implications for regulatory evaluation and implementation. NAMs framework, formalized through the FDA Modernization Act 2.0 (Han 2023), authorizes scientifically valid alternatives to animal testing and encourages the adoption of AI-based models and advanced in vitro systems (FDA 2025). However, regulatory acceptance remains contingent upon demonstrated reliability, comprehensive uncertainty quantification, and clearly defined context-of-use specifications (FDA 2025).

Regulatory frameworks are progressively adapting to incorporate model-informed approaches into drug development. The FDA's Model-Informed Drug Development paired meeting pilot program, established under the Prescription Drug User Fee Act VI, provides a structured mechanism for sponsors to engage in early discussions with review teams regarding modeling strategies, focusing on model qualification, verification, and context-specific validation (Madabushi et al. 2022). Similarly, EMA guideline on PBPK modeling (2018) specifies expectations for model documentation, verification, and fit-for-purpose validation, differentiating between models intended for drug–drug interaction prediction and those used for dose selection or optimization (EMA 2018).

Context-dependent regulatory requirements further increase the complexity of model acceptance. For FIH dose escalation, conservative assumptions are essential because overestimating clearance can pose significant safety risks (Reigner and Blesch 2002; Zou et al. 2012). In contrast, early compound screening allows broader predictive tolerances, with acceptable deviations typically ranging within two- to three-fold of observed values (Abduljalil et al. 2014; Zhang et al. 2015). Consequently, validation thresholds differ according to the specific application and the associated risk level within the drug development continuum.

For AI-based and OoC-derived predictions, the central issue is not the methodology itself but whether the model demonstrates sufficient credibility and reliability within its defined context of use. Challenges related to dataset bias, limited external validation, restricted interpretability, and inadequate uncertainty quantification currently limit their independent regulatory acceptance. For instance, clearance overestimation resulting from training set bias could lead to unsafe FIH dose selection, thereby necessitating confirmatory validation through PBPK modeling or the adoption of conservative dose margins. Consequently, existing regulatory frameworks position these emerging approaches as

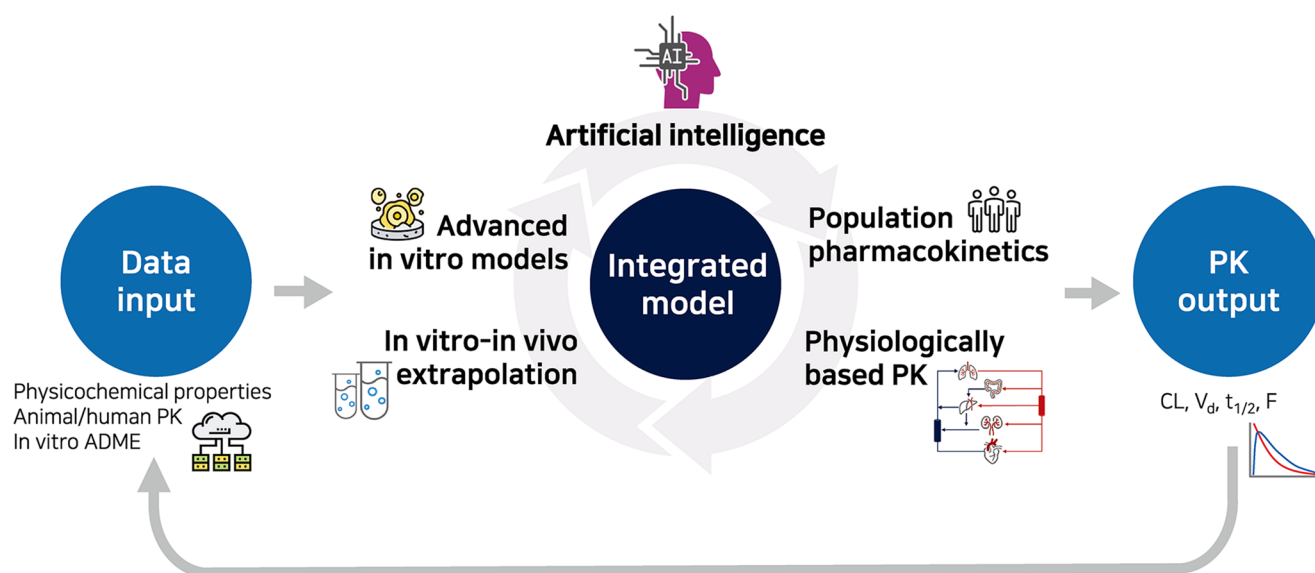


Fig. 5 Integrated framework of complementary methodologies for human PK prediction. Data flow originates from physicochemical properties and in vitro ADME measurements through multiple interconnected pathways. AI/ML models provide predicted parameters (CL and V_d) that feed into mechanistic PBPK frameworks. Advanced in

vitro systems generate physiologically relevant parameters (CL_{int} and permeability) for IVIVE and PBPK integration. Outputs from these methods converge through population-PK or PBPK modeling to produce final PK predictions (CL, V_d , $t_{1/2}$, and F)

complementary and supportive tools, best applied within integrated modeling workflows to augment mechanistic PBPK analyses rather than replace them.

Toward integrated approaches in human PK prediction

Given the cross-cutting challenges and evolving regulatory considerations discussed above, the broader adoption of model-informed PK approaches will depend less on the emergence of entirely new technologies and more on how existing methodologies are strategically integrated within decision-making workflows (Fig. 5). Rather than replacing established frameworks, these emerging approaches are expected to gain regulatory traction when applied as complementary components that strengthen existing lines of evidence.

Hybrid modeling strategies represent a pragmatic path forward. AI-based models can support parameter estimation, identify covariate relationships, and inform sensitivity analyses within mechanistic PBPK frameworks—thereby improving efficiency while addressing concerns related to interpretability and extrapolation. Likewise, advanced in vitro systems demonstrate greatest value when their outputs are explicitly aligned with defined biological questions, such as informing specific parameters or validating mechanistic assumptions, rather than being positioned as comprehensive substitutes for clinical data. Advancing this integrative vision requires progress in four key domains.

First, standardized validation datasets containing well-curated compound panels with consistent PK endpoints are essential for enabling meaningful cross-method benchmarking. Second, external validation protocols that specify temporal or structural data-splitting criteria are necessary to rigorously assess the generalizability of AI and ML models. Third, reproducibility standards that address inter-laboratory variability in OoC systems—including cell sourcing, microchip fabrication, and flow rate conditions—will accelerate regulatory confidence and facilitate comparability. Fourth, integrated reporting guidelines outlining documentation requirements for multi-method predictions, including uncertainty quantification and applicability domain definitions, will enhance transparency and streamline regulatory review. Practical implementation of model-informed PK prediction is expected to evolve progressively across different stages of drug development. During early discovery, rapid AI-based screening can be combined with allometric estimates to prioritize candidate compounds for further evaluation. As molecules advance into the optimization phase, AI-predicted parameters can be incorporated directly into mechanistic PBPK frameworks to refine translational projections. For regulatory submissions, validated PBPK models with comprehensive parameterization provide both mechanistic transparency and predictive accuracy, supporting evidence-based decision-making. Taken together, the near-term future of human PK prediction lies not in convergence toward a single dominant methodology but in the disciplined integration of complementary tools, each applied

within a clearly defined and scientifically justified context of use.

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Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Statement of human and animal rights This article does not contain any studies with human and animal subjects performed by any of the authors.

Conflict of interest S. Shin was the associate editor of the Journal of Pharmaceutical Investigation while conducting this study. Editor status has no bearing on editorial considerations. Other authors (N. Choi and B.S. Shin) declare that they have no conflict of interest.

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