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ADVANCES IN LIPID NANOPARTICLE-BASED DERMAL DELIVERY: FORMULATION, CHARACTERIZATION, AND THERAPEUTIC APPLICATIONS OF SOLID LIPID NANOPARTICLES AND NANOSTRUCTURED LIPID CARRIERS.

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ABSTRACT

Physiologically Based Pharmacokinetic (PBPK) modeling has emerged as a powerful mechanistic approach in drug development, enabling the quantitative prediction of drug absorption, distribution, metabolism, and excretion (ADME) based on physiological, biochemical, and drug-specific parameters. Unlike traditional empirical models, PBPK integrates anatomical and physiological realism with in vitro and in vivo data, allowing extrapolation across species, populations, and dosing conditions. This review provides a comprehensive overview of the current status of PBPK modeling, highlighting its fundamental principles, structural components, and key inputs, including physiological and drug-specific parameters. The applications of PBPK modeling across the drug development continuum are discussed, with emphasis on early drug discovery, candidate selection, dose optimization, drug–drug interaction prediction, and evaluation in special populations. The increasing acceptance of PBPK modeling by regulatory agencies has further strengthened its role in supporting regulatory submissions and labeling decisions. In addition, the integration of PBPK with advanced computational approaches such as artificial intelligence, machine learning, and quantitative systems pharmacology has significantly enhanced its predictive capabilities and expanded its application in precision medicine. The utility of PBPK modeling in addressing the complexities associated with biologics and advanced drug delivery systems is also examined. Despite its advantages, challenges related to data availability, model validation, and computational complexity persist, necessitating continued methodological advancements and standardization. Overall, PBPK modeling represents a transformative tool in pharmaceutical research, offering a cost-effective and scientifically robust platform for improving drug development efficiency and clinical outcomes.

Keywords: Physiologically Based Pharmacokinetics (PBPK); Drug Development; Pharmacokinetic Modeling; Model-Informed Drug Development (MIDD)

INTRODUCTION

Physiologically Based Pharmacokinetic (PBPK) modeling has emerged as a powerful and mechanistically driven computational approach that plays a pivotal role in modern drug development.

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Unlike traditional compartmental pharmacokinetic models, PBPK models integrate physiological, biochemical, and drug-specific data to simulate the absorption, distribution, metabolism, and excretion (ADME) of pharmaceutical compounds within the human body. These models are structured based on realistic anatomical compartments representing organs and tissues, interconnected by blood flow, enabling a more

biologically relevant prediction of drug behavior across different populations and clinical scenarios. The increasing complexity of drug molecules, including poorly soluble compounds, biologics, and targeted therapies, has necessitated the adoption of advanced modeling tools such as PBPK to improve prediction accuracy and reduce the reliance on extensive *in vivo* studies (Yang & Zhang, 2022). One of the key advantages of PBPK modeling lies in its ability to extrapolate data from preclinical studies to humans through *in vitro*–*in vivo* extrapolation (IVIVE), thereby facilitating early decision-making in drug discovery and development. Furthermore, PBPK models are extensively used to predict pharmacokinetics in special populations such as pediatrics, geriatrics, and patients with organ impairment, where clinical trials may be limited or ethically challenging. In recent years, regulatory agencies including the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have increasingly recognized the value of PBPK modeling in supporting regulatory submissions, particularly for drug–drug interaction (DDI) assessments, dose optimization, and labeling recommendations. The integration of PBPK with emerging technologies such as artificial intelligence (AI), machine learning, and quantitative systems pharmacology (QSP) has further expanded its capabilities, allowing for more robust simulations and personalized medicine approaches. Despite these advancements, challenges remain, including the availability and quality of input data, model validation complexities, and the need for standardized methodologies (Lale et al., 2024). Nevertheless, PBPK modeling continues to evolve as a critical tool that bridges the gap between experimental research and clinical application, offering a cost-effective and time-efficient strategy for optimizing drug development pipelines. This review aims to provide a comprehensive overview of the current status of PBPK modeling, its applications in drug development and regulatory science, associated challenges, and future directions in the era of precision medicine.

Concept and Principles of PBPK Modeling

Physiologically Based Pharmacokinetic (PBPK) modeling is a mechanistic modeling approach that quantitatively describes the absorption, distribution, metabolism, and excretion (ADME) of drugs using mathematical representations of human physiology and drug-specific properties. The core concept of PBPK modeling lies in its ability to simulate drug kinetics through anatomically realistic compartments corresponding to organs and tissues, each defined by physiological parameters such as tissue volume, blood flow rates, and composition. These compartments are interconnected via the circulatory system, enabling dynamic prediction of drug concentration–time profiles

in plasma and individual tissues. Unlike empirical compartmental models, which rely primarily on observed data, PBPK models are grounded in biological plausibility, allowing extrapolation across species, dosing regimens, and patient populations (Du & Liu, 2024). The principles of PBPK modeling are based on mass balance equations, where the rate of drug movement into and out of each compartment is governed by physiological processes and drug-specific parameters, including partition coefficients, permeability, and metabolic clearance. Drug absorption is modeled based on the route of administration, considering factors such as gastrointestinal transit, solubility, and permeability for oral drugs, or skin permeability in transdermal delivery systems. Distribution is characterized using tissue-to-plasma partition coefficients, which reflect drug affinity for different tissues, while metabolism and excretion are incorporated through enzyme kinetics and organ-specific clearance pathways, primarily involving the liver and kidneys. A fundamental strength of PBPK modeling is its reliance on *in vitro* and *in silico* data, which can be integrated through *in vitro*–*in vivo* extrapolation (IVIVE) to predict human pharmacokinetics early in drug development (Gaohua et al., 2023). Additionally, PBPK models account for interindividual variability by incorporating demographic, genetic, and pathological differences, making them highly valuable for simulating drug behavior in diverse populations. The mechanistic nature of PBPK modeling also allows for the evaluation of complex scenarios such as drug–drug interactions, altered physiology in disease states, and the impact of formulation strategies on drug disposition. Over the years, advances in computational tools and availability of physiological databases have significantly enhanced the development and application of PBPK models. Consequently, PBPK modeling has become an indispensable component of modern pharmaceutical research, providing a robust framework for understanding drug disposition, optimizing dosing strategies, and supporting regulatory decision-making (Gonnabathula et al., 2025).

Structure and Components of PBPK Models

The structure and components of Physiologically Based Pharmacokinetic (PBPK) models are designed to represent the human body as a series of interconnected physiological compartments that mimic real anatomical organs and tissues. Each compartment corresponds to a specific organ such as the liver, kidney, lungs, heart, brain, adipose tissue, and muscle, and is defined by key physiological parameters including tissue volume, blood flow rate, and tissue composition. These compartments are linked through arterial and venous blood circulation, forming a dynamic system that enables the prediction of drug movement throughout the body over time. A central component of PBPK models is the blood compartment,

which serves as the primary transport medium for drug distribution between organs. The model distinguishes between arterial and venous blood to accurately simulate drug delivery and return from tissues. Within each tissue compartment, drug distribution is governed by tissue-to-plasma partition coefficients, which reflect the affinity of the drug for that specific tissue based on its physicochemical properties such as lipophilicity, ionization, and protein binding. Another critical component is the absorption module, which varies depending on the route of administration. For oral delivery, the gastrointestinal tract is represented by multiple segments, each accounting for drug dissolution, permeability, and first-pass metabolism. For other routes such as intravenous, transdermal, or inhalational delivery, specific absorption pathways are incorporated accordingly. The liver plays a central role in metabolism and is modeled using enzyme kinetic parameters, often incorporating cytochrome P450-mediated biotransformation processes, while the kidneys are responsible for drug excretion through filtration, secretion, and reabsorption mechanisms. Additionally, PBPK models may include specialized compartments such as the blood-brain barrier to simulate central nervous system drug delivery, or placental compartments in pregnancy models. Binding components, including plasma protein binding and tissue binding, are integrated to determine the free fraction of the drug available for distribution and elimination (Bellini, 2024). Advanced PBPK models may also incorporate nonlinear kinetics, transporter-mediated processes, and time-dependent changes in enzyme activity. Furthermore, variability in physiological parameters can be introduced to simulate different populations such as pediatric, geriatric, or diseased individuals. Overall, the structure of PBPK models is highly modular and flexible, allowing the integration of diverse biological, chemical, and clinical data to generate comprehensive and predictive simulations of drug disposition, making them a powerful tool in pharmaceutical research and development.

Physiological and Drug-Specific Parameters

Physiological and drug-specific parameters form the foundational inputs of Physiologically Based Pharmacokinetic (PBPK) models, enabling accurate simulation of drug disposition within the human body. Physiological parameters describe the biological system and include organ and tissue volumes, regional blood flow rates, tissue composition (lipid, water, and protein content), and physiological characteristics such as pH and enzyme expression levels. These parameters are typically

derived from anatomical and physiological databases and can be adjusted to reflect variability across populations, including age, gender, ethnicity, and disease states. For instance, hepatic blood flow and enzyme activity may differ significantly between healthy individuals and patients with liver impairment, influencing drug metabolism and clearance. Similarly, renal function parameters such as glomerular filtration rate (GFR) are critical for modeling drug excretion, especially for renally cleared compounds. In addition to system-specific inputs, drug-specific parameters characterize the physicochemical and biochemical properties of the compound and play a crucial role in determining its pharmacokinetic behavior (Ambikadevi & Subha Hency Jose, 2021). These include molecular weight, lipophilicity ($\log P$ or $\log D$), ionization constant (pK_a), aqueous solubility, and permeability, all of which influence drug absorption and tissue distribution. Plasma protein binding and tissue binding parameters determine the fraction of unbound drug available for pharmacological activity and clearance. Furthermore, intrinsic clearance values derived from *in vitro* studies, such as liver microsomes or hepatocytes, are used to estimate metabolic rates via *in vitro*–*in vivo* extrapolation (IVIVE). Transporter-mediated processes, including uptake and efflux transporters like P-glycoprotein and organic anion transporting polypeptides (OATPs), are increasingly recognized as important drug-specific parameters that can significantly affect drug disposition, particularly in organs such as the liver, intestine, and brain (Taskar et al., 2021). The integration of these physiological and drug-specific inputs within PBPK models allows for a mechanistic representation of ADME processes, enabling predictions of drug concentration–time profiles in plasma and tissues under various scenarios. Moreover, these parameters facilitate extrapolation across species and support simulations in special populations, such as pediatrics or patients with comorbidities. Sensitivity analysis is often employed to identify the most influential parameters, helping to refine model accuracy and guide experimental design. Overall, the precise characterization and integration of physiological and drug-specific parameters are essential for the robustness and predictive capability of PBPK models, making them indispensable tools in drug development and regulatory science.

Table 1: Key Physiological and Drug-Specific Parameters in PBPK Modeling

Category	Parameter	Description	Role in PBPK Modeling
Physiological	Organ volume	Size of tissues/organs	Determines drug distribution capacity
Physiological	Blood flow rate	Perfusion rate to organs	Controls drug delivery kinetics
Physiological	Tissue composition	Lipid, water, protein content	Influences partitioning behavior
Physiological	Enzyme expression	CYP450 levels	Affects metabolism rate
Physiological	GFR (Glomerular Filtration Rate)	Renal filtration capacity	Determines renal clearance
Drug-specific	Molecular weight	Size of drug molecule	Affects permeability and distribution
Drug-specific	Lipophilicity (log P/log D)	Drug solubility in lipids	Influences membrane permeability
Drug-specific	pKa	Ionization constant	Determines absorption and distribution
Drug-specific	Plasma protein binding	% bound drug	Controls free drug concentration
Drug-specific	Intrinsic clearance (CL _{int})	Metabolic rate	Governs hepatic metabolism
Drug-specific	Permeability	Ability to cross membranes	Affects absorption

Absorption, Distribution, Metabolism, and Excretion (ADME) Inputs

Absorption, distribution, metabolism, and excretion (ADME) inputs constitute the core mechanistic drivers of Physiologically Based Pharmacokinetic (PBPK) models, enabling a comprehensive and biologically realistic prediction of drug disposition within the body. Absorption parameters define the rate and extent to which a drug enters systemic circulation and are highly dependent on the route of administration. For orally administered drugs, key inputs include solubility, dissolution rate, intestinal permeability, gastrointestinal transit time, pH-dependent ionization, and first-pass metabolism in the gut wall and liver. Advanced PBPK models may incorporate segmental absorption models such as the advanced compartmental absorption and transit (ACAT) model to simulate region-specific drug uptake. In the case of transdermal, inhalational, or parenteral routes, specific permeability coefficients and delivery kinetics are incorporated. Distribution inputs describe the movement of the drug between systemic

circulation and tissues and are governed by factors such as tissue-to-plasma partition coefficients, plasma protein binding, blood-to-plasma ratio, and tissue composition. (Sakre & Dubey, 2024) These parameters determine the extent of drug penetration into various organs, including specialized compartments such as the brain, where the blood–brain barrier significantly influences drug entry. Metabolism inputs focus primarily on hepatic biotransformation, although extrahepatic metabolism in tissues such as the intestine, kidney, and lungs may also be relevant. Key parameters include intrinsic clearance (CL_{int}), enzyme kinetics (K_m and V_{max}), and enzyme abundance, particularly for cytochrome P450 isoforms such as CYP3A4, CYP2D6, and CYP2C9. These inputs are often derived from in vitro systems such as liver microsomes or hepatocytes and extrapolated to in vivo conditions using IVIVE approaches. Additionally, transporter-mediated metabolism and enzyme induction or inhibition are incorporated to simulate complex drug–drug interactions. Excretion inputs describe the elimination of the drug and

its metabolites from the body, primarily through renal and biliary pathways. Renal excretion parameters include glomerular filtration rate, tubular secretion, and reabsorption processes, while biliary excretion involves hepatic transporters such as P-glycoprotein and multidrug resistance-associated proteins (MRPs). (Fagerholm, 2023) The integration of these ADME inputs within PBPK models allows for dynamic simulation of drug concentration–time profiles across different tissues and physiological conditions. Furthermore, these inputs enable the prediction of pharmacokinetic variability in special populations and under pathological conditions, such as renal or hepatic impairment. Overall, accurate characterization and integration of ADME parameters are essential for the predictive performance and clinical relevance of PBPK models in drug development.

Applications of PBPK Modeling in Drug Development

Physiologically Based Pharmacokinetic (PBPK) modeling has become an indispensable tool in drug development, offering a mechanistic framework to support decision-making across the entire pharmaceutical lifecycle. One of its primary applications lies in early drug discovery, where PBPK models are used to predict human pharmacokinetics from preclinical data, enabling the selection and optimization of promising drug candidates. By integrating physicochemical properties and in vitro data, PBPK modeling facilitates in vitro–in vivo extrapolation (IVIVE), thereby reducing reliance on animal studies and accelerating development timelines. During the preclinical and clinical phases, PBPK models are extensively employed for dose selection and optimization by simulating various dosing regimens and predicting systemic exposure under different conditions. This is particularly valuable in first-in-human studies, where safety and efficacy must be carefully balanced. Another critical application is the prediction of drug–drug interactions (DDIs), where PBPK models simulate enzyme inhibition or induction, as well as transporter-mediated interactions, to assess the potential impact of co-administered drugs on pharmacokinetics (Lale et al., 2024). Regulatory agencies increasingly accept PBPK-based DDI predictions as supportive evidence, sometimes reducing the need for dedicated clinical interaction studies. PBPK modeling also plays a vital role in evaluating pharmacokinetics in special populations, including pediatric, geriatric, pregnant, and organ-impaired patients, where clinical trials may be limited due to ethical or logistical constraints. By incorporating physiological variability and disease-specific changes, PBPK models enable tailored dosing recommendations for these populations. Furthermore, PBPK approaches are widely used in formulation development to assess the impact of drug delivery systems, such as modified-release formulations or nanocarriers, on drug absorption and bioavailability. In the later stages of drug

development, PBPK modeling supports regulatory submissions by providing evidence for dose justification, labeling recommendations, and risk assessment. It is also utilized in bridging studies to extrapolate data across different populations or dosage forms, thereby minimizing the need for additional clinical trials (Perry et al., 2020). With the integration of advanced computational tools, including artificial intelligence and machine learning, PBPK modeling is increasingly contributing to precision medicine by enabling individualized therapy based on patient-specific characteristics. Overall, the versatility and predictive capability of PBPK modeling make it a powerful and cost-effective approach that enhances efficiency, reduces development risks, and supports informed decision-making throughout the drug development process.



Figure:1 Applications of PBPK Modeling in Drug Development

Early Drug Discovery and Candidate Selection

Early drug discovery and candidate selection represent critical stages in the pharmaceutical development pipeline, where Physiologically Based Pharmacokinetic (PBPK) modeling has emerged as a valuable tool for guiding informed decision-making. During this phase, a large number of potential compounds are screened for their pharmacokinetic and pharmacodynamic properties, and PBPK models provide a mechanistic framework to predict how these compounds will behave in the human body before clinical testing. By integrating drug-specific physicochemical properties such as solubility, permeability, lipophilicity, and ionization with biological parameters, PBPK modeling enables the simulation of absorption, distribution, metabolism, and excretion (ADME) profiles. This allows researchers to identify compounds with favorable pharmacokinetic characteristics and eliminate those with poor bioavailability, rapid clearance, or high variability at an early stage, thereby reducing attrition rates in later phases of development. One of the key advantages of PBPK modeling in early discovery is its ability to perform in vitro-in vivo extrapolation (IVIVE), where experimental data from cell-based assays, microtomes, or recombinant enzymes are translated into predicted human pharmacokinetics (Yang & Zhang, 2022). This approach minimizes the reliance on extensive animal studies and accelerates the transition from preclinical to clinical development. Additionally, PBPK models can simulate various dosing scenarios and routes of administration, helping to optimize drug design and formulation strategies. For instance, compounds with low solubility can be evaluated for potential formulation enhancements, such as lipid-based systems or nanoparticle delivery, to improve systemic exposure. PBPK modeling also supports the assessment of drug-drug interaction potential by predicting the involvement of metabolic enzymes and transporters early in development, allowing for structural modifications to reduce interaction risks. Furthermore, the incorporation of population variability into PBPK models enables the evaluation of how different physiological conditions may influence drug disposition, providing insights into potential safety concerns. The integration of PBPK modeling with computational tools such as quantitative structure-activity relationship (QSAR) models and molecular docking further enhances candidate selection by linking pharmacokinetics with pharmacological activity (Perry et al., 2020). As a result, PBPK modeling facilitates a more rational and efficient drug discovery process by prioritizing compounds with optimal pharmacokinetic profiles, reducing development costs, and improving the likelihood of clinical success. Overall, its application in early drug discovery and candidate selection significantly contributes to the advancement of safer and more effective therapeutic agents.

Regulatory Guidelines and Acceptance

Regulatory guidelines and acceptance of Physiologically Based Pharmacokinetic (PBPK) modeling have evolved significantly over the past decade, reflecting the growing confidence of global regulatory agencies in model-informed drug development (MIDD) approaches. Agencies such as the U.S. Food and Drug Administration, European Medicines Agency, and Pharmaceuticals and Medical Devices Agency have established frameworks and guidance documents that outline the appropriate use of PBPK modeling in regulatory submissions. These guidelines emphasize the scientific rigor, transparency, and validation of PBPK models to ensure their reliability in predicting pharmacokinetic outcomes. PBPK modeling is now widely accepted for various regulatory applications, including the prediction of drug-drug interactions (DDIs), dose optimization, pediatric extrapolation, and assessment of pharmacokinetics in special populations. One of the most prominent areas of regulatory acceptance is the use of PBPK models to support DDI risk assessment, where simulations can replace or reduce the need for dedicated clinical studies, particularly when evaluating enzyme inhibition or induction involving cytochrome P450 isoforms and drug transporters. Regulatory agencies require that PBPK models be thoroughly validated using available clinical data, with clear documentation of model assumptions, parameter sources, and sensitivity analyses to demonstrate robustness (Tegenge et al., 2025). In addition, the concept of “fit-for-purpose” modeling is emphasized, meaning that the level of model complexity and validation should align with the intended regulatory application. The U.S. Food and Drug Administration has published specific guidance on the use of PBPK modeling in regulatory submissions, encouraging its integration into new drug applications (NDAs) and biologics license applications (BLAs), particularly for informing labeling decisions and risk management strategies. Similarly, the European Medicines Agency supports PBPK modeling for pediatric investigation plans (PIPs) and bridging studies, facilitating extrapolation across populations and formulations. The increasing use of PBPK modeling in regulatory contexts has also been driven by advancements in software platforms, availability of physiological databases, and improved understanding of enzyme and transporter kinetics. Despite its growing acceptance, challenges remain in standardizing model evaluation criteria and ensuring consistency across regulatory agencies (Johnson et al., 2021). Nevertheless, PBPK modeling has become a critical component of modern regulatory science, enabling more efficient drug development by reducing uncertainty, minimizing the need for extensive clinical trials, and supporting evidence-based decision-making. As regulatory

frameworks continue to evolve, PBPK modeling is expected to play an even more prominent role in advancing precision medicine and accelerating the approval of safe and effective therapeutic products.

Case Studies of Regulatory Submissions

Case studies of regulatory submissions have demonstrated the practical value and increasing acceptance of Physiologically Based Pharmacokinetic (PBPK) modeling in supporting drug approval processes and informing labeling decisions. Regulatory agencies such as the U.S. Food and Drug Administration and the European Medicines Agency have reviewed numerous submissions in which PBPK models were used to address critical pharmacokinetic questions, particularly in the context of drug–drug interactions (DDIs), dose optimization, and special population studies. One notable example involves the use of PBPK modeling to predict CYP3A4-mediated DDIs, where sponsors employed mechanistic models to simulate the impact of enzyme inhibitors or inducers on drug exposure. In several cases, these predictions were accepted by regulatory agencies as sufficient evidence, reducing or eliminating the need for dedicated clinical DDI studies. Similarly, PBPK modeling has been successfully used to support pediatric dose selection by extrapolating adult pharmacokinetic data to pediatric populations, taking into account age-dependent physiological changes such as organ maturation, enzyme expression, and body composition (Peters, 2021). This approach has facilitated the development of pediatric dosing recommendations without extensive clinical trials, aligning with ethical considerations. Another important application highlighted in regulatory case studies is the use of PBPK modeling in assessing the impact of hepatic or renal impairment on drug pharmacokinetics. By incorporating disease-specific physiological changes, PBPK models have enabled sponsors to simulate drug exposure in impaired populations and justify dose adjustments in product labeling. Additionally, PBPK modeling has been applied in biowaiver justifications and formulation bridging, where differences in drug release profiles or formulation characteristics are evaluated without conducting additional *in vivo* bioequivalence studies. Regulatory submissions have also demonstrated the utility of PBPK modeling in evaluating complex scenarios involving transporter-mediated interactions and nonlinear pharmacokinetics. In many of these cases, the success of PBPK-based submissions has depended on the robustness of the model, including thorough validation against clinical data, transparent reporting of assumptions, and comprehensive sensitivity analyses (Freriksen et al., 2023). The concept of “fit-for-purpose” modeling has been central to regulatory acceptance, ensuring that the model is appropriately designed for its intended application. Overall, these case

studies illustrate that PBPK modeling is not only a supportive tool but also a decision-enabling approach that can streamline drug development, reduce costs, and enhance regulatory confidence. As experience with PBPK modeling continues to grow, it is expected that its role in regulatory submissions will expand further, contributing to more efficient and scientifically informed approval processes.

Integration with Artificial Intelligence and Machine Learning

The integration of artificial intelligence (AI) and machine learning (ML) with Physiologically Based Pharmacokinetic (PBPK) modeling represents a transformative advancement in model-informed drug development, enabling more accurate, efficient, and scalable predictions of drug behavior. Traditional PBPK models rely heavily on experimentally derived physiological and drug-specific parameters, which may be limited by data availability and variability; however, AI and ML techniques can enhance these models by identifying complex, nonlinear relationships within large datasets and generating predictive insights from high-dimensional data. Machine learning algorithms, such as random forests, support vector machines, and deep neural networks, can be employed to predict key pharmacokinetic parameters including tissue-to-plasma partition coefficients, intrinsic clearance, and permeability, thereby reducing the dependency on extensive *in vitro* or *in vivo* experiments. Additionally, AI-driven approaches can facilitate automated parameter optimization and model calibration, significantly improving the efficiency of PBPK model development. (Chou & Lin, 2022) The integration of ML with PBPK also supports the analysis of big data from diverse sources, including omics datasets, clinical trial data, electronic health records, and real-world evidence, enabling the development of more personalized and population-specific models. For example, AI can be used to stratify patient populations based on genetic, demographic, or disease-specific factors, allowing PBPK models to simulate individualized pharmacokinetic responses and support precision medicine initiatives. Furthermore, hybrid modeling approaches that combine mechanistic PBPK frameworks with data-driven ML models offer enhanced predictive performance by leveraging the strengths of both methodologies. AI can also aid in the identification of drug–drug interaction risks by analyzing patterns in enzyme and transporter activity, while natural language processing (NLP) tools can extract relevant pharmacokinetic information from scientific literature to inform model inputs. Despite these advantages, challenges remain in integrating AI and ML with PBPK modeling, including issues related to data quality, model interpretability, and regulatory acceptance. Ensuring transparency and explainability of AI-driven

predictions is essential, particularly in regulatory contexts where decision-making must be scientifically justified (Mayer et al., 2023). Nevertheless, the convergence of AI, ML, and PBPK modeling holds significant promise for revolutionizing drug development by enabling faster, more accurate, and cost-effective prediction of pharmacokinetics, ultimately improving therapeutic outcomes and advancing the field toward a more data-driven and personalized approach to medicine.

Systems Pharmacology and Quantitative Systems Pharmacology (QSP)

Systems pharmacology and Quantitative Systems Pharmacology (QSP) represent advanced, integrative approaches that extend beyond traditional pharmacokinetic and pharmacodynamic modeling by incorporating complex biological networks and mechanistic understanding of drug action at multiple scales. While PBPK models primarily focus on the absorption, distribution, metabolism, and excretion (ADME) of drugs, QSP integrates these pharmacokinetic processes with pharmacodynamic responses, cellular signaling pathways, and disease progression models to provide a holistic representation of drug–biological system interactions. Systems pharmacology combines principles from systems biology, pharmacology, and computational modeling to analyze how drugs influence biological networks, including gene expression, protein interactions, and metabolic pathways. QSP models are typically constructed using a combination of differential equations and data-driven approaches, enabling the simulation of dynamic interactions between drugs and targets across different biological levels, from molecular to organ systems. One of the key advantages of QSP is its ability to capture the complexity of disease mechanisms and predict therapeutic outcomes under various conditions, including combination therapies and long-term treatment scenarios. (Mody et al., 2025) This is particularly valuable in complex and multifactorial diseases such as cancer, cardiovascular disorders, and neurodegenerative diseases, where multiple pathways and feedback mechanisms are involved. The integration of PBPK and QSP models allows for a seamless connection between drug exposure and biological response, facilitating the prediction of dose–response relationships and optimization of therapeutic regimens. For instance, PBPK models can provide time-dependent drug concentration profiles in specific tissues, which serve as inputs for QSP models to simulate downstream pharmacological effects. Additionally, QSP models can incorporate patient-specific factors such as genetic variability, disease state, and biomarker profiles, supporting the development of personalized medicine strategies. The application of systems pharmacology and QSP in drug development spans various stages, including target identification, biomarker discovery, dose selection,

and clinical trial design. These models also enable virtual clinical trials, where different patient populations and treatment scenarios can be simulated to assess efficacy and safety outcomes. Despite their potential, challenges in QSP modeling include the need for extensive and high-quality biological data, model complexity, and computational demands. Furthermore, regulatory acceptance of QSP models is still evolving, requiring standardized methodologies and validation frameworks. Nevertheless, systems pharmacology and QSP are increasingly recognized as powerful tools that enhance the understanding of drug mechanisms, improve prediction of clinical outcomes, and support more rational and efficient drug development processes.

Model Complexity and Computational Challenges

Model complexity and computational challenges represent significant considerations in the development and application of Physiologically Based Pharmacokinetic (PBPK) models, particularly as these models become increasingly detailed and data-intensive. PBPK models are inherently complex due to their mechanistic nature, incorporating numerous physiological compartments, each defined by multiple parameters such as tissue volumes, blood flow rates, partition coefficients, and biochemical processes. As the number of compartments and parameters increases, the mathematical structure of the model becomes more intricate, often involving large systems of nonlinear differential equations that require advanced numerical methods for solution. This complexity can lead to increased computational demands, especially when simulating multiple dosing scenarios, conducting sensitivity analyses, or performing population-based simulations that account for interindividual variability (Radeva-Ilieva & Georgiev, 2020). Furthermore, the integration of additional biological processes such as transporter-mediated kinetics, enzyme induction and inhibition, and time-dependent changes in physiology further compounds the computational burden. One of the major challenges associated with complex PBPK models is parameter uncertainty, as many physiological and drug-specific inputs may not be directly measurable and must be estimated or derived from limited experimental data. This can lead to issues with parameter identifiability, where multiple parameter sets produce similar model outputs, making it difficult to determine the true underlying values. Additionally, model overparameterization can reduce robustness and increase the risk of overfitting, particularly when the model is calibrated using sparse clinical data. Computational challenges also arise in the context of model optimization and validation, where iterative processes are required to refine model predictions and ensure consistency with observed data. These processes can be time-consuming and resource-intensive,

particularly for large-scale models or when incorporating variability across populations. The use of high-performance computing and parallel processing techniques has helped to mitigate some of these challenges, enabling faster simulations and more efficient exploration of parameter space. However, the need for specialized software tools and computational expertise can limit accessibility for some researchers. Moreover, ensuring numerical stability and convergence of solutions remains a critical concern, particularly in models with stiff equations or complex feedback mechanisms. Despite these challenges, ongoing advancements in computational algorithms, software platforms, and data integration techniques continue to improve the feasibility and reliability of PBPK modeling. Addressing model complexity and computational limitations is essential for enhancing the predictive performance and practical applicability of PBPK models in drug development and regulatory science.

PBPK in Biologics and Complex Drug Products

Physiologically Based Pharmacokinetic (PBPK) modeling for biologics and complex drug products has gained increasing importance as the pharmaceutical landscape shifts toward macromolecules and advanced formulations that exhibit distinct pharmacokinetic behaviors compared to small-molecule drugs. Biologics, including monoclonal antibodies, recombinant proteins, peptides, and nucleic acid-based therapeutics, are characterized by large molecular size, structural complexity, and unique disposition mechanisms such as target-mediated drug disposition (TMDD), receptor binding, and intracellular trafficking. Unlike small molecules that primarily rely on passive diffusion, biologics often exhibit limited tissue permeability and are distributed via convection through the lymphatic system, requiring specialized PBPK frameworks that incorporate vascular and interstitial spaces, lymph flow, and endothelial transport processes. Additionally, Fc receptor-mediated recycling, particularly through the neonatal Fc receptor (FcRn), plays a critical role in prolonging the half-life of many therapeutic antibodies, and this mechanism must be explicitly modeled to accurately predict systemic exposure. For complex drug products such as liposomes, nanoparticles, antibody–drug conjugates (ADCs), and long-acting injectables, PBPK models must account for both the carrier system and the active pharmaceutical ingredient, including release kinetics, degradation, and interactions with biological barriers. These systems often exhibit nonlinear pharmacokinetics due to saturation of transporters or binding sites, necessitating the incorporation of nonlinear equations and mechanistic descriptions of biological processes. Furthermore, immunogenicity and the formation of anti-drug antibodies (ADAs) can significantly alter the pharmacokinetics of biologics,

adding another layer of complexity to PBPK modeling. The development of PBPK models for biologics relies on integrating *in vitro*, preclinical, and clinical data, including binding affinities, internalization rates, and tissue-specific expression of targets and receptors. Such models are increasingly used to support dose selection, optimize dosing regimens, and predict pharmacokinetics in special populations. Regulatory agencies are also recognizing the value of PBPK modeling for biologics, particularly in the context of biosimilar development, where models can support comparability assessments and reduce the need for extensive clinical studies. Despite these advancements, challenges remain in accurately parameterizing models due to limited availability of data on tissue distribution and biological interactions. Nevertheless, PBPK modeling continues to evolve as a critical tool for understanding the complex pharmacokinetics of biologics and advanced drug delivery systems, enabling more efficient development and improved therapeutic outcomes.

CONCLUSION

Physiologically Based Pharmacokinetic (PBPK) modeling has firmly established itself as a transformative and indispensable tool in modern drug development, bridging the gap between experimental pharmacology and clinical application through a mechanistic, systems-based framework. By integrating physiological, biochemical, and drug-specific data, PBPK models enable a comprehensive understanding of absorption, distribution, metabolism, and excretion (ADME) processes, offering predictive insights that are not easily achievable through traditional empirical approaches. Throughout the drug development continuum—from early discovery and candidate selection to clinical trials and regulatory submissions—PBPK modeling has demonstrated its versatility in optimizing dosing strategies, predicting drug–drug interactions, and supporting decision-making in special populations such as pediatrics, geriatrics, and patients with organ impairments. Its capacity to perform *in vitro*–*in vivo* extrapolation (IVIVE) has significantly reduced reliance on animal studies, thereby accelerating development timelines and aligning with ethical considerations in pharmaceutical research. Furthermore, the growing acceptance of PBPK modeling by regulatory authorities has reinforced its value as a scientifically robust and reliable approach for risk assessment, labeling recommendations, and regulatory approvals, particularly when models are developed and validated following fit-for-purpose principles. The integration of PBPK modeling with emerging technologies such as artificial intelligence (AI), machine learning (ML), and quantitative systems pharmacology (QSP) has further expanded its capabilities, enabling more accurate parameter estimation, model optimization, and simulation

of complex biological interactions. These hybrid approaches facilitate the incorporation of large-scale datasets, including real-world evidence and omics data, paving the way for personalized medicine and digital twin applications. In addition, PBPK modeling has proven particularly valuable in addressing the challenges associated with biologics and complex drug products, where traditional pharmacokinetic models fall short due to nonlinear kinetics, target-mediated drug disposition, and intricate delivery mechanisms. By accommodating such complexities, PBPK models provide a more realistic representation of drug behavior, supporting the development of innovative therapies such as monoclonal antibodies, nanoparticles, and gene-based treatments. Despite these advancements, several challenges remain that must be addressed to fully realize the potential of PBPK modeling. These include limitations in the availability and quality of physiological and drug-specific data, uncertainties in parameter estimation, and the inherent complexity of model structures, which can pose computational and interpretational challenges. Standardization of modeling practices, validation criteria,

and reporting guidelines is essential to ensure consistency and reproducibility across studies and regulatory submissions. Moreover, enhancing the transparency and interpretability of models, particularly when integrated with AI and ML techniques, is critical for gaining broader acceptance among stakeholders, including clinicians, researchers, and regulatory authorities. Continued investment in high-quality experimental data generation, development of user-friendly modeling platforms, and interdisciplinary collaboration will be key to overcoming these limitations. Looking ahead, the future of PBPK modeling is closely aligned with the evolution of precision medicine and model-informed drug development (MIDD). The concept of patient-specific modeling, supported by digital health technologies and real-time data integration, holds promise for individualized therapy optimization and improved clinical outcomes. PBPK models are also expected to play a central role in virtual clinical trials, enabling the simulation of diverse patient populations and treatment scenarios, thereby reducing the need for extensive and costly clinical studies.

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