MULTIDISCIPLINARY JOURNAL OF INSTRUCTION (MDJI)

www. https://journal.mdji.org/ Vol. 7No. 1 (2024)

Integration of Physiologically Based Pharmacokinetic (PBPK) Modeling with IVIVC for Precision Dosing

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Abstract

Precision dosing aims to optimize therapeutic outcomes by tailoring drug administration to individual patient characteristics. Physiologically Based Pharmacokinetic (PBPK) modeling has emerged as a powerful tool for predicting drug absorption, distribution, metabolism, and excretion based on physiological and biochemical parameters. In parallel, In Vitro–In Vivo Correlation (IVIVC) facilitates the translation of in vitro drug dissolution data to in vivo performance, traditionally aiding in formulation development and regulatory decisions. Integrating PBPK modeling with IVIVC represents a promising strategy to enhance predictive accuracy in pharmacokinetics and support model-informed precision dosing. This article explores the scientific rationale, methodologies, and practical applications of this integrated approach. We discuss how the synergy between PBPK and IVIVC can improve drug development efficiency, reduce the need for extensive clinical trials, and enable personalized therapeutic regimens. Additionally, we highlight current challenges, such as data requirements and regulatory acceptance, and provide a forward-looking perspective on advancements in computational pharmacology that may further empower this integration.

Keywords: Physiologically Based Pharmacokinetic (PBPK) Modeling, In Vitro–In Vivo Correlation (IVIVC), Precision Dosing, Model-Informed Drug Development (MIDD), Pharmacokinetics, Drug Absorption, Personalized Medicine,Biopharmaceutics, Regulatory Science, Simulation and Modeling.

1. Introduction

Precision dosing has become a cornerstone of modern pharmacotherapy, driven by the need to tailor drug administration to individual patient characteristics to optimize therapeutic outcomes and minimize adverse effects. This paradigm shift is especially critical in the context of narrow therapeutic index drugs, complex disease states, and heterogeneous patient populations such as pediatrics, geriatrics, and those with organ impairment. Achieving true precision in dosing requires a robust understanding of drugs' pharmacokinetics (PK) and pharmacodynamics (PD) and their variability across different physiological conditions (Bermejo et al., 2020).

Physiologically Based Pharmacokinetic (PBPK) modeling has emerged as a powerful computational approach that simulates drug absorption, distribution, metabolism, and excretion (ADME) using mechanistic representations of human physiology and drug-specific properties. Unlike traditional compartmental models, PBPK models incorporate anatomical, physiological, and biochemical parameters, enabling the simulation of drug behavior in various subpopulations and pathological states. PBPK modeling has been increasingly adopted in both industry and regulatory settings for tasks such as first-in-human dose prediction, drug-drug interaction assessment, and pediatric extrapolation.

Parallel to PBPK modeling, In Vitro–In Vivo Correlation (IVIVC) has long been a valuable tool in pharmaceutical development, primarily for establishing relationships between in vitro drug release and in vivo performance. IVIVC serves as a surrogate for bioequivalence studies and

helps in optimizing drug formulations, particularly for oral solid dosage forms. By predicting clinical performance from laboratory data, IVIVC can reduce the need for extensive in vivo testing, thereby accelerating drug development timelines.

Despite their merits, both PBPK modeling and IVIVC face limitations when used in isolation. IVIVC often relies on empirical correlations that may not fully account for inter-individual variability or complex physiological interactions. Conversely, PBPK models, while mechanistic, can be constrained by incomplete or uncertain input data. Integrating these two methodologies offers a synergistic approach that leverages the predictive power of PBPK models with the empirical foundation of IVIVC. This integration facilitates a more comprehensive understanding of drug behavior, especially in scenarios where traditional methods fall short.

The primary objective of this article is to explore the scientific and practical basis for integrating PBPK modeling with IVIVC to support precision dosing. We will discuss the conceptual framework, methodological considerations, regulatory perspectives, and real-world applications of this integrated approach. Additionally, we will highlight challenges, current limitations, and future opportunities, including the potential role of advanced analytics and machine learning in refining predictive models. By synthesizing insights from both domains, this article aims to inform and advance the development of model-informed precision dosing strategies.

2. Fundamentals of PBPK Modeling

2.1 Definition and Components

Physiologically Based Pharmacokinetic (PBPK) modeling is a mechanistic modeling approach that simulates the ADME (absorption, distribution, metabolism, and excretion) processes of drugs using mathematical representations of human or animal physiology. Each PBPK model comprises compartments that correspond to real anatomical organs and tissues, interconnected by blood flow. Drug-specific properties such as solubility, permeability, binding affinity, and metabolic rates are integrated with physiological parameters like organ volumes, blood flow rates, and enzyme expression levels to simulate drug kinetics across the body.

2.2 Key Physiological Parameters

PBPK models depend on a wide array of physiological parameters that may vary by age, gender, disease state, or ethnicity (Balhara, Kale, & Singh, 2022). These include cardiac output, tissue composition (e.g., fat, muscle, water), organ-specific blood flows, and enzyme/transporter abundances. Such parameters can be tailored to specific populations (e.g., pediatric, geriatric, or renal-impaired) to predict how physiological differences influence drug kinetics. This makes PBPK particularly powerful for extrapolating dosing regimens across diverse groups.

2.3 Advantages Over Traditional PK Models

Unlike empirical compartmental models, PBPK models offer a mechanistic framework that enhances extrapolative capabilities beyond the data used for model development. This includes predicting outcomes in untested scenarios such as drug-drug interactions, special populations, and different routes of administration. Furthermore, PBPK models can integrate in vitro data and preclinical findings, making them a versatile tool across all stages of drug development. Their transparency and physiological relevance also support better regulatory confidence and decision-making (Najjar et al., 2022).

2.4 Applications in Drug Development and Regulation

PBPK modeling is increasingly used throughout the drug development lifecycle—from early-stage candidate selection to late-phase clinical trial support and regulatory submissions.

Applications include first-in-human dose prediction, formulation design, assessing the impact of hepatic or renal impairment, and supporting biowaivers. Regulatory agencies like the U.S. FDA, EMA, and PMDA now accept PBPK analyses as part of model-informed drug development (MIDD) strategies, reinforcing the method's credibility and utility.

3. Overview of IVIVC

3.1 Levels of IVIVC (A, B, and C)

In Vitro–In Vivo Correlation (IVIVC) refers to the establishment of a predictive relationship between a drug's in vitro dissolution characteristics and its pharmacokinetic performance. The U.S. FDA classifies IVIVC into three levels:

- **Level A** represents a point-to-point correlation between in vitro dissolution and the entire plasma drug concentration-time profile, offering the highest predictive power.

- **Level B** uses statistical moment analysis (e.g., mean residence time, AUC) but does not establish a direct, one-to-one correlation.

Level C relates a single PK parameter (e.g., Cmax or AUC) to a single point of in vitro data, and is the least robust.
Level A is generally preferred for regulatory purposes, particularly for bioequivalence waivers and formulation changes (Ozbek, Genc, & Ulgen, 2024).

3.2 Development Process of IVIVC

The development of an IVIVC typically involves generating multiple formulations with varying release rates, conducting in vitro dissolution studies, and correlating these with in vivo pharmacokinetic data from clinical studies. Regression analysis or deconvolution methods are used to model the relationship (More & Tade, 2025). Once validated, the model allows prediction of in vivo performance from in vitro tests, which can streamline development and reduce the need for additional human trials.

3.3 Regulatory Relevance and Acceptance

IVIVC has long been recognized by regulatory agencies as a valuable tool in supporting biowaivers, managing post-approval formulation changes, and reducing the burden of clinical testing (Guo et al., 2018). When a validated Level A IVIVC is in place, it may be used to justify modifications in formulation without the need for further bioequivalence studies. This regulatory acceptance supports cost efficiency and accelerates time to market.

3.4 Limitations of IVIVC in Isolation

Despite its benefits, IVIVC is not universally applicable. Its utility is often limited to oral solid dosage forms with well-characterized dissolution behavior. Moreover, it assumes that in vitro conditions can adequately mimic the in vivo environment—an assumption that may not hold for drugs with complex absorption mechanisms or significant first-pass metabolism. IVIVC also lacks the flexibility to account for patient-specific variability, which limits its standalone use in precision dosing (Patel & Patel, 2024).

4. Rationale for Integration of PBPK and IVIVC

4.1 Bridging In Vitro Data with Complex Physiological Systems

While IVIVC provides a useful empirical bridge between in vitro dissolution and in vivo drug performance, it often oversimplifies the complex physiological processes involved in drug absorption and disposition. PBPK modeling, by contrast, offers a mechanistic representation of these processes (Stillhart et al., 2019). Integrating PBPK with IVIVC allows for a more holistic prediction of in vivo drug behavior based on in vitro data, enhancing the relevance of dissolution studies by contextualizing them within the body's physiological framework.

4.2 Enhancing Predictability of Drug Absorption and Bioavailability

Drug absorption is influenced by multiple factors, including gastrointestinal pH, enzyme activity, transporter expression, and regional permeability. IVIVC alone may not account for these variables, especially in patients with altered physiology. By incorporating PBPK models, which simulate these physiological variations, the integrated approach can improve the predictability of drug absorption and systemic exposure, making it more reliable across different populations and clinical scenarios.

4.3 Case for Model-Informed Drug Development (MIDD)

Regulatory bodies increasingly advocate for Model-Informed Drug Development (MIDD) to support evidence-based decision-making. The integration of PBPK and IVIVC aligns with this paradigm by combining empirical and mechanistic modeling to enhance the quality and efficiency of drug development. It facilitates rational formulation design, optimized clinical trial planning, and more confident extrapolation to special populations—all of which support regulatory submissions and lifecycle management(Corpstein & Li, 2023).

4.4 Addressing Variability in Special Populations

Standard IVIVC models are typically derived from healthy volunteer data and may not accurately reflect drug performance in populations with different physiological or pathological characteristics. PBPK modeling addresses this gap by simulating drug kinetics in varied demographics, such as children, the elderly, or patients with hepatic or renal impairment. The integration of IVIVC-derived dissolution data into PBPK models enables a patient-centered approach to dosing, improving therapeutic outcomes and safety in these vulnerable groups.

5. Methodologies for Integration

5.1 Workflow for Combined PBPK-IVIVC Modeling

The integration of PBPK and IVIVC involves a systematic workflow:

1. **Data Collection**: Gather in vitro dissolution profiles and pharmacokinetic data from clinical or preclinical studies.

2. **Develop IVIVC Model**: Use regression or deconvolution methods to establish the relationship between in vitro dissolution and in vivo performance.

3. **Construct PBPK Model**: Develop a physiologically based model incorporating anatomical, physiological, and drug-specific parameters.

4. **Integrate IVIVC Data**: Input the dissolution parameters from the IVIVC model into the PBPK framework to simulate systemic drug exposure.

5. **Validation and Refinement**: Compare model predictions against observed data and refine parameters as needed to ensure accuracy and robustness.

5.2 Software Platforms and Computational Tools

Several computational platforms facilitate the integration of PBPK and IVIVC, including:

- **Simcyp Simulator**: Widely used for PBPK modeling, with features to integrate dissolution data.
- **GastroPlus**: A tool for mechanistic absorption modeling, offering seamless integration of IVIVC.
- **PK-Sim**: An open-source platform for PBPK modeling with flexible customization options.

These tools allow for advanced simulations, sensitivity analyses, and population-specific predictions.

5.3 Data Requirements and Validation Criteria

The success of PBPK-IVIVC integration depends on the quality and comprehensiveness of input data. Required datasets include:

- **In Vitro Data**: High-resolution dissolution profiles across different media (e.g., pH variations).
- **In Vivo Data**: Plasma concentration-time profiles from multiple formulations.

Validation criteria involve demonstrating the ability of the integrated model to predict key pharmacokinetic parameters such as Cmax, Tmax, and AUC with acceptable accuracy, typically within ±10-15% of observed values.

5.4 Handling Uncertainty and Sensitivity Analysis

Model predictions can be affected by variability and uncertainty in physiological parameters, dissolution data, or drug-specific inputs (Golhar et al., 2023). Sensitivity analyses are essential to identify critical parameters influencing model outputs. Monte Carlo simulations and uncertainty quantification methods are often employed to evaluate confidence in predictions and ensure robust decision-making.

6. Case Studies and Applications

6.1 Successful Integration in Regulatory Submissions

The integration of PBPK and IVIVC has gained traction in regulatory science, with several cases demonstrating its utility in drug approval and post-approval changes. For example, the U.S. FDA has accepted PBPK-IVIVC models to support biowaivers and justify formulation changes without additional in vivo studies. One notable case involved a modified-release formulation where the PBPK model, enriched with IVIVC-derived dissolution inputs, reliably predicted clinical performance and reduced the need for human trials, leading to regulatory acceptance (Dabke et al., 2023).

6.2 Use in Generic Drug Development

Generic manufacturers often face the challenge of demonstrating bioequivalence to innovator products. Integrated PBPK-IVIVC models have been successfully used to simulate bioequivalence scenarios, allowing developers to fine-tune formulations based on predictive in vitro dissolution data (Cheng et al., 2025). This approach streamlines development and minimizes trial-and-error experimentation, especially for Biopharmaceutics Classification System (BCS) Class II and IV drugs, where dissolution and absorption are critical (Bouzom, Ball, Perdaems, & Walther, 2012).

6.3 Personalized Medicine and Dose Adjustment

In clinical settings, PBPK-IVIVC models have been used to support individualized therapy by predicting how a formulation will behave in specific patient populations. For instance, in oncology or pediatrics, where patient physiology can significantly alter drug kinetics, integrated models have enabled dose adjustments tailored to metabolic capacity or organ function. This is particularly useful in narrow therapeutic index drugs, where small changes in exposure can lead to toxicity or treatment failure (Anand, Pepin, Kolhatkar, & Seo, 2022).

6.4 Model-Based Biowaivers

Model-based biowaivers represent a major application of PBPK-IVIVC integration. Instead of conducting full-scale clinical studies, developers can leverage predictive modeling to demonstrate that a new formulation performs equivalently to an approved one. This has been applied to support scale-up and post-approval changes (SUPAC) and global harmonization efforts, saving time and reducing development costs while maintaining regulatory compliance (Loisios-Konstantinidis & Dressman, 2020).

7. Challenges and Limitations

7.1 Data Gaps and Quality Issues

One of the primary challenges in the integration of PBPK and IVIVC is the dependence on high-quality input data. In vitro dissolution tests must be conducted under biorelevant conditions that closely mimic the gastrointestinal environment, including variations in pH, bile salts, and motility (Kostewicz et al., 2014). However, standardized dissolution methods may not fully capture this complexity, leading to inaccurate or non-predictive dissolution profiles. Similarly, in vivo pharmacokinetic data are often limited to healthy volunteers, which may not represent the target patient population. Variability in patient physiology, enzyme activity, and transporter expression further complicates model parameterization. Missing or inconsistent physiological parameters—such as tissue partition coefficients, enzyme kinetics, or blood flow rates—can undermine the reliability of PBPK models. Ensuring comprehensive and representative datasets is therefore critical but often resource-intensive.

7.2 Computational Complexity

PBPK models require the integration of multiple physiological compartments, each governed by differential equations that describe drug kinetics in organs and tissues. When combined with IVIVC, which adds an empirical dissolution layer, the models become increasingly complex. This complexity demands advanced computational platforms, high processing power, and specialized expertise in pharmacometrics and systems pharmacology. The iterative process of model development, parameter estimation, and validation can be time-consuming and computationally expensive. Moreover, model complexity can introduce challenges in transparency and interpretability, potentially limiting wider adoption among clinicians and decision-makers unfamiliar with such modeling approaches (Kollipara et al., 2024).

7.3 Regulatory Acceptance and Standardization

While regulatory agencies such as the FDA, EMA, and PMDA have issued guidance encouraging the use of PBPK modeling and IVIVC, there is still a lack of universally accepted standards for integrating these approaches. Regulatory expectations regarding model validation, sensitivity analyses, and reporting vary across jurisdictions, creating uncertainty for developers. Furthermore, the absence of harmonized criteria for acceptable predictive performance can delay regulatory acceptance. The evolving nature of model-informed drug development (MIDD) frameworks means that sponsors must proactively engage with regulators early in development to align on modeling strategies. Establishing clear, consensus-driven guidelines and best practices remains an ongoing need to facilitate smoother regulatory pathways.

7.4 Integration with Real-World Data

The current PBPK-IVIVC models primarily rely on controlled clinical trial data, which may not fully capture the complexity of real-world patient populations. Factors such as patient adherence, concomitant medications, lifestyle differences, and disease progression can profoundly affect drug exposure and response. Incorporating these real-world variables into integrated models is challenging due to data heterogeneity, quality issues, and privacy concerns. However, advances in digital health technologies, electronic health records, and wearable devices offer promising avenues for enriching models with real-world evidence. Successfully integrating these data could enhance the precision and applicability of dosing recommendations, particularly for chronic diseases and complex therapeutic areas, but will require significant methodological innovations and validation efforts.

8. Future Directions

8.1 Integration with Artificial Intelligence and Machine Learning

The future of PBPK and IVIVC integration lies in leveraging artificial intelligence (AI) and machine learning (ML) to enhance model development and predictive power. AI algorithms can analyze large datasets to identify complex, nonlinear relationships between in vitro and in vivo data, optimize model parameters, and uncover hidden patterns in pharmacokinetics. ML techniques may also automate sensitivity analyses and parameter tuning, significantly reducing model development time and improving accuracy. Integrating AI-driven tools with mechanistic PBPK-IVIVC models holds promise for creating adaptive models that continuously learn from new data, thereby refining precision dosing strategies in real-time.

8.2 Expanding Applications in Personalized Medicine

As healthcare shifts towards individualized treatment, PBPK-IVIVC models are expected to play a pivotal role in personalized medicine. Incorporating patient-specific genetic, physiological, and environmental factors into integrated models will enable truly tailored dosing regimens. For example, pharmacogenomic data can be combined with physiological parameters to predict individual drug metabolism and response. This expansion will require development of user-friendly platforms that clinicians can apply in routine practice to guide therapy, improving efficacy and safety on a patient-by-patient basis.

8.3 Enhanced Model Validation Through Big Data

The increasing availability of real-world data (RWD) and real-world evidence (RWE) offers an unprecedented opportunity to validate and refine integrated PBPK-IVIVC models. Large-scale patient data from electronic health records, registries, and post-marketing surveillance can be used to verify model predictions in diverse populations and real-life scenarios. This approach

will strengthen confidence in model-informed decision-making and facilitate broader regulatory acceptance. Collaborative initiatives among academia, industry, and regulatory agencies will be crucial to develop standardized methodologies for RWD integration.

8.4 Development of Regulatory Frameworks and Guidelines

To fully realize the potential of integrated PBPK-IVIVC modeling, regulatory frameworks must evolve to provide clear, harmonized guidance on model development, validation, and reporting. International cooperation among regulatory bodies can lead to consensus standards that foster innovation while ensuring patient safety. Incorporating feedback from stakeholders, including industry and academia, will be essential in creating pragmatic and flexible policies that accommodate rapid technological advances.

8.5 Integration with Other Modeling Approaches

Future research may focus on combining PBPK-IVIVC integration with other quantitative methods such as pharmacodynamic (PD) modeling, systems pharmacology, and quantitative systems toxicology. Such multi-scale modeling approaches can provide comprehensive insights into drug efficacy, safety, and variability. This holistic perspective will improve the robustness of precision dosing strategies and support personalized therapy across complex therapeutic areas like oncology, neurology, and infectious diseases.

9. Conclusion

The integration of Physiologically Based Pharmacokinetic (PBPK) modeling with In Vitro–In Vivo Correlation (IVIVC) represents a significant advancement in the pursuit of precision dosing. By combining the mechanistic, physiology-driven insights of PBPK models with the empirical predictive power of IVIVC, this integrated approach offers a more comprehensive understanding of drug behavior in diverse populations and complex clinical scenarios. It enhances the ability to predict in vivo drug performance from in vitro data, streamlines drug development, supports regulatory decisions, and paves the way for personalized medicine.

Despite challenges such as data quality, computational complexity, and regulatory variability, ongoing technological advancements—including artificial intelligence, real-world data integration, and evolving regulatory frameworks—promise to overcome these barriers. The continued refinement and broader adoption of integrated PBPK-IVIVC modeling will empower researchers, clinicians, and regulators to optimize dosing regimens with greater confidence, ultimately improving therapeutic outcomes and patient safety.

As precision dosing becomes an integral part of modern pharmacotherapy, the synergy between PBPK and IVIVC will be essential in transforming drug development and clinical practice toward more individualized and effective treatments.

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