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PHARMACOKINETIC–PHARMACODYNAMICS MODELING IN MODERN DRUG DEVELOPMENT

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ABSTRACT

Pharmacokinetic–pharmacodynamic (PK–PD) modelling is now a foundational tool in modern drug development, linking drug exposure to pharmacologic response to aid dose optimisation, efficacy, and safety. By integrating pharmacokinetics (absorption, distribution, metabolism, excretion) with pharmacodynamics (receptor-binding, dose–response, mechanistic signalling), PK–PD models enable data-driven decision-making in preclinical and clinical phases. Mechanism-based and population PK–PD approaches—including physiologically based (PBPK) and target-mediated disposition models—allow prediction across species, disease states, and subpopulations. Regulatory agencies such as the U.S. FDA and EMA recognize model-informed drug development (MIDD) as key to trial design, dose selection and approval. Emerging advances—including artificial intelligence, quantitative systems pharmacology (QSP), and real-world data integration—are enhancing model predictive power and supporting precision medicine. This review discusses current methodologies, applications, regulatory perspectives, and future directions in PK–PD modelling, underlining its role in accelerating efficient, patient-centered drug development.

KEYWORDS: Pharmacokinetics, pharmacodynamics, PK–PD modelling, model-informed drug development, physiologically based pharmacokinetics, precision medicine.

INTRODUCTION

The discovery of novel methods to control drug absorption and disposal in order to achieve a desired effect is the main focus of drug delivery research. Drug delivery systems with increasingly intricate structures are created as technology develops.[1-2] so the methods of drug absorption and disposal following the administration of such drug delivery devices

become incredibly intricate. It includes an organized set of preclinical, clinical, regulatory, and discovery phases, all of which are intended to guarantee that novel therapeutic candidates are both beneficial to patients and backed by science. When choosing a biological pathway or transmitter implicated in the course of a disease as a therapeutic target, the procedure usually starts by target identification and confirmation.[3-4] Then, using contemporary methods like molecular docking, high-throughput screening, and computer modeling, lead compounds are found and refined to improve their pharmacological activity or ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties. When a lead compound shows promising properties, it moves on to preclinical research, where its pharmacokinetic and toxicological profiles are evaluated in vitro and in vivo.[5-6] The chemical proceeds to clinical trials, which are carried out in successive phases (Phase I–III), following a successful preclinical review in order to determine safety, dose, and therapeutic activity in humans. Before the medication is released into the market, the completed data are sent for regulatory assessment & approval. Post-marketing monitoring (phase IV) keeps an eye on long-term safety and effectiveness in a real-world environment even after approval. Pharmacokinetic and pharmacodynamic (PK-PD) modeling has frequently sped up the creation of these molecules and been used to help choose the dosage schedule.[7-8] This idea particularly gains from the application of more complex models that combine the concentration-effect characteristics (PD) of the drug response with the time-concentration characteristics (PK) of a possible medication. Pharmacokinetic–pharmacodynamic (PK–PD) modeling has emerged as a key instrument in this method in the past few years. PK–PD modelling helps anticipate treatment results, optimize dose regimes, and cut down on the time and expense of clinical development by computationally connecting drug concentrations to their physiological effects. In a consequence, PK-PD modeling improves decision-making, enables tailored treatment, and raises overall therapeutic rates in contemporary drug discovery.[9-10] The use of PK-PD modeling in the creation of mAbs is growing in popularity.[11-12]

Basics of Pharmacokinetics (PK)

Absorption

The mechanisms by which a foreign substance enters the body's systemic circulation are known as absorption processes.[13-14] Although absorption through the lungs, which is crucial for chemical compounds and materials found in pollutants and dust particles, and the skin, which serves as the primary barrier between the internal milieu and the external environment, can also take place, the gastrointestinal tract is the most significant site of absorption. Therapeutic efficacy is directly impacted by appropriate bioavailability, which is ensured by efficient absorption.

Distributed

Drugs are distributed from the bloodstream to different tissues after absorption. Blood flow rates, tissue permeability, plasma protein binding, and the drug's physicochemical characteristics—such as its ionization and lipophilicity—all affect distribution. The liver, the kidneys, and heart are among the organs with high blood flow that initially get higher medication concentrations. Therapeutics for the nervous system in general may be impacted by barriers such as the blood–brain barrier that limit drug access into particular tissues.

Metabolism

Medicines undergo mostly hepatic metabolism, which changes them into more hydrophilic metabolites to aid in excretion. Phase I reactions (oxidation, reduction, and hydrolysis) and Phase II reactions (conjugation) are the two general categories into which metabolic processes fall. Cytochrome P450 isoforms, along with additional enzymes are

crucial for these changes. Drug metabolism can result in metabolites with changed pharmacological properties, inactivate the pharmaceutical ingredient, or activate prodrugs.

Excretion

Drugs and their metabolites are expelled from the body by excretion, primarily through renal clearance. These mechanisms, which are impacted by renal function, urine pH, and the drug's physicochemical properties, include glomerular filtering, tubular secretion, and passive reabsorption. The pulmonary, perspiration, saliva, breast milk, biliary/fecal, and other secondary excretion pathways all contribute differently to the total amount of medication cleared. Patients with renal or liver disease require cautious dose modification since impaired excretion can result in drug buildup and toxicity.[15-17]

Basics of Pharmacodynamics (PD)

It is widely acknowledged that pharmacokinetic-pharmacodynamics modeling (PK-PD) and simulation are essential for increasing the effectiveness of the drug-development process, which is beset by high attrition rates.[18-19] Pharmaceutical corporations, academic institutions, and regulatory bodies have all promoted the use of PK and PD modeling over the years in order to better understand medication efficacy and safety and, consequently, improve the quality of decision making in drug development.This will lower the chance of attrition during clinical development because of ineffectiveness or safety. Mechanism-based PK-PD model has become a crucial tool in translation drug research, helping to advance early (preclinical and discovery) insights into the safety and effectiveness of drugs into the clinical development stage. In contrast to empirical PK-PD models, mechanism-based PK-PD models statistically describe certain steps in the causality chain connecting drug administration and effect. Mechanism-based PK-PD models, on the other hand, are distinct from fully mechanistic or systems biology models. Mechanism-based PK-PD modeling employs a data-driven top-down methodology that begins with a minimal descriptive level and then adds more complexity to gain a deeper understanding of the system. As a result, these models' parameters are composites of the real pharmacological and physiological processes. However, systems biology models are bottom-up, starting at the level of molecular routes, and are intrinsically comprehensive and fully mechanistic.[20-21]

Dose-response relationship

The dose-response relationship describes the way a drug's effect varies with different doses. A dose-response curve, which graphs the drug concentration against the observed effect, is frequently used to illustrate this relationship. Key variables consist of: **Emax**: The drug's highest possible effect.

EC50: The drug's potency is indicated by the concentration at which 50% of the maximum effect is produced. Higher values of the hill coefficient, which measures how steep the dose-response curve is, suggest that an effect is greater with slight dose adjustments.

Transduction of Signals and Receptor Binding

Drugs work by attaching themselves to particular receptors and starting a series of intracellular processes called signal transduction.

Usually, receptors have two primary domains:

Ligand-binding domain: Where the drug binds.

Effector domain: The area where a biological reaction is triggered by binding.

Depending on the type of medication and receptor, this binding can either activate or inhibit different signaling pathways. For instance, binding to G-protein-coupled receptors can alter intracellular cyclic AMP levels, which may affect smooth muscle contraction and heart rate.

THE INTEGRATION OF PHARMACOKINETICS/ PHARMACODYNAMICS

The PK and PD approaches are effective instruments for characterizing and comprehending how drugs work in whole organisms. In clinical pharmacology, where investigations of drug biodisposition and activity must be comparatively noninvasive and reasonably safe. Each offers an alternate viewpoint on how the medication behaves pharmacologically in the patient. Nevertheless, when used separately, they present an incomplete picture that reduces their use in clinical and research settings.[22] By bridging the separate sets of data and removing the need to assume a relationship between dose and dosage or concentration and effect, as is inherent in the usage of each tool alone, the combined use of PK and PD substantially boosts the power and utility of these tools.[23-24] The PK and PD approaches are effective instruments for characterizing and comprehending how drugs work in whole organisms. In clinical pharmacology, where investigations of drug biodisposition and activity must be comparatively noninvasive and reasonably safe. Each offers an alternate viewpoint on how the medication behaves pharmacologically in the patient. Even when used separately, they present an incomplete picture that reduces their use in clinical and research settings. By bridging the separate sets of data and removing the need to assume a relationship between dose and dosage or concentration and effect, as is inherent in the usage of each tool by itself, the combined use of PK and PD substantially boosts the effectiveness and utility of these tools.It is possible to employ integrated PK/PD investigations to ascertain the evaluation of the length and extent of exposure and effect in relation to disease severity, as well as the impact of disease on the combined disposition and response profile.[25-26] These kinds of investigations can also shed light on human physiology. PK/PD investigations of a humanized clotting factor serve as an example of this, offering a model for comprehending the rates of host protein formation and circulation through offering a more thorough understanding of the relationship between exogenously administered and endogenously synthesized proteins.When developing a novel medication, it is very helpful to simultaneously assess the dose-exposure and exposure-response relationships for outcomes of interest. Early in the development of new drugs, these interactions can be predicted and perhaps used to improve the efficacy and safety of late-phase clinical trials. For instance, in a combined PK/PD study of an experimental S-adenosylmethionine decarboxylase inhibitor, the researchers were able to determine the single PK parameter that was the greatest sensitive predictor of the neutrophil count nadir and the percentage decrease in neutrophil count in response to treatment by pooling data from three studies with different dosing regimens.[27-28] The dose schedule with the lowest risk of toxicity for upcoming clinical trials was subsequently selected using these findings. The same method can also be used prospectively to predict response in a clinical context with limited sampling techniques if there is enough information to show such a link.A model to forecast the total body exposure of an anthracycline tumor fighting medicine from a single-point concentration measure was created and verified in a related study. Leukocyte nadir was subsequently estimated using the computed exposure estimate following medication administration.The anticipated parameters and the outcome of interest (toxicity in these circumstances) showed a correlation between 0.6 and 0.7 in both investigations.[29-30] The PK/PD models give the researcher and clinician a more palatable way to reduce the risk for exposure-associated adverse events than empiric dose adjustment, even though this suggests that a small percentage of the variability in the dose-response relationship is still unaccounted for.[31] The integration of PK and PD can

differentiate the independent exposure-response relationships for the effects of interest in medicines that have numerous pharmacologic/physiologic effects. For instance, the time course and amount of exposure necessary to elicit the psychomotor and amnesic effects of benzodiazepines might be distinguished by comparing multiple estimates of PK/PD parameters. The amount of medication and method of administration needed for the same agent to produce various exposures and, consequently, various response profiles can be determined using PK/PD experiments. Using this method, researchers examined how giving the same synthetic antagonist affected the suppression of two distinct endogenous hormones (such as testosterone and LH) in terms of both duration and magnitude.[32-33] The impact of food impacts on a drug's exposure profile can also be outlined using PK/PD studies. In order to forecast the extent of change in both therapeutic outcome variables (such as blood pressure and heart rate) and undesirable outcomes (such as orthostasis, HA, and flushing), the food-drug interaction of a special formulation of a dihydropyridine calcium channel blocker was described in this study.[34-35] The PK/PD connections, once they are established, can provide information about complex drug-drug interactions. Infection with the human immunodeficiency treatment mostly depends on PK/PD data to take advantage of drug-drug interactions for the patient's benefit by using or avoiding combinations of medications that may influence exposure and virologic response rates .Additionally, they enable the clinician to assess and predict how drug-drug interactions would affect drug use and activity in situations where coadministration is unavoidable, such as in the Recurrent seizure syndromes in a case.Static determinations of PK/PD connections cannot be anticipated to give the clinician all the information they ultimately need in order to optimize drug therapy, as was covered in the sections on limitations above.[36-37] When illness and disposition are changing, the patient's struggle is still a serious worry. The numerous PK/PD trials with levodopa in the treatment of Parkinson's disease, which offer a startling example of how the two processes alter along a continuum as the patients as well as their disease progress, may serve as the greatest example of this.[38] As Parkinson's disease worsens as individuals age, the rate at which drugs move into and out of the effect site decreases, the duration of therapy response shortens, the effect magnitude decreases, the concentrations needed to reach 50% of maximal activity rise, the PK/PD curve slopes steeper, and the curve shifts to the right . It goes beyond saying that extrapolating combined PK/PD data from a group of patients at a single stage of their illness to a group of patients at a different stage would result in inaccurate conclusions.[39-40]

Types of PK–PD Models

Pharmacokinetic–pharmacodynamic (PK–PD) models can be broadly divided into three categories: population-centered, empirical, and mechanistic. These models vary in terms of physiological analysis, data requirements, and complexity. The time course of pharmacological effects in response to concentration can be described and predicted using such models, which are crucial tools.

Empirical Frameworks

The observed relationship between drug concentration and effect is described by empirical models, which may or may not take into consideration the underlying biological mechanisms. The sigmoid Emax model, which uses the Hill coefficient to capture the inclination of the concentration–response curve, the Emax model, which specifies the maximum effect that can be achieved, and linear or log-linear models, that are appropriate for characterizing proportional or logarithmic relationships between concentration and response, are common examples. Because of their ease of use and adaptability, these models are frequently employed for preliminary characterisation of pharmacological action.

Models of Mechanisms

Mechanistic models depict the causal processes that connect drug exposure to response through the integration of physiological and biochemical concepts. When a medicine affects the synthesis or depletion of an endogenous mediator instead of directly affecting it, this is referred to as an indirect response model. Target-mediated drug disposition (TMDD) models take into consideration nonlinear kinetics brought on by high-affinity binding of the drug and pharmacological targets, whereas turnover model capture the dynamic equilibrium between the production and breakdown of biological components. For biologics and medications with saturable binding mechanisms, these models are essential.

Population PK–PD Models

Quantifying individual differences in drug exposure and response within a community is the goal of population models. The most popular method for estimating fixed as well as random effects that enables prediction across several patient subgroups is nonlinear mixed-effects modeling, which is utilized in software like NONMEM. Further, extrapolation across species, age groups, and illness situations is made possible by physiologically based pharmacokinetic (PBPK) models, which offer a mechanistic framework based on physiological and anatomical characteristics. Personalized healthcare and regulatory submissions are using these models more and more.[41-42]

Applications in Modern Drug Development

Quantitative and translational methods are crucial to modern drug research in order to increase productivity and lower clinical failure rates. Preclinical–clinical translation, which uses in vitro and in vivo data to forecast human pharmacokinetics and pharmacodynamics and hence identify viable drug candidates prior to clinical trials, is one crucial use. Dosage optimization throughout Phase I–III trials is another crucial element. Confirmatory trials are conducted to determine the best dosage and reduce side effects after initial safety and tolerability studies in healthy subjects (Phase I) advance to efficacy and dose refinement in patients (Phase II).In addition, therapeutic drug monitoring (TDM) and bioequivalence studies are crucial for maintaining drug concentrations within therapeutic windows, especially for medications with limited safety margins, and guaranteeing that generic formulations offer exposure comparable to that of brand-name medications. Finally, because pediatric and geriatric populations differ physiologically, simulation and modeling techniques have made it possible to develop safer and more efficient dosing strategies while lowering the practical and ethical obstacles associated with extensive clinical testing. When taken as a whole, these uses highlight the value of population-specific, quantitative, and translational approaches in contemporary drug development, improving both efficacy and safety.[43-44]

Tools and Software in Modern Drug Development

Pharmacokinetic (PK) and pharmacodynamic (PD) modeling now relies heavily on a range of data analysis, dosage optimization, and accurate simulation programs and systems.created by Sheiner and Belin in 1972 [] NONMEM is still widely used today, having received widespread support in both academia and the pharmaceutical sector. The word NONMEM yielded 1334 results in a recent PubMed search (performed in May 2012). 1023 results were obtained by using the phrases population pharmacokinetics AND NONMEM. Between 2002 and 2004, NONMEM was used in 69% of population pharmacokinetic studies that were assessed. Pmetrics (MM-USCPACK), Phoenix NLME (WinNonLin), and MONOLIX, for example, yielded 26, 5, or 156 hits, respectively, when searched on PubMed. Pmetrics (MM-USCPACK), Phoenix NLME (WinNonLin), and MONOLIX, for example, yielded 26, 5, and 156 hits,

respectively, when queried on PubMed.[45-46] Globomax purchased the software's license rights in 2001, and as of 2006, it was still a part of Icon Development. A set of algorithms that can perform approximate likelihood, exact maximum likelihood, and nonparametric analysis (FO, FOCE, FOCE with eta-epsilon interaction [FOCEI], FOCE centered, Laplace, Markov Chain Monte Carlo [MCMC]SAEM, and nonparametric analysis) are included in the current version of NONMEM (version 7.2.0). It has more support groups than other software products because it has been on the market for more than 30 years. But using NONMEM is more appropriate for the more seasoned, skilled user and takes a great deal of experience.[47]

MONOLIX®

The Monolix Group, a five-person academic scientific team founded in 2003 with assistance from the pharmaceutical sector, produced MONOLIX. Lixoft is the license holder for the most recent version (4.0), which was published in October 2011. SAEM, combined with MCMC for maximum likelihood estimation, is the main algorithm used by MONOLIX. The SAEM method uses a "exact" stochastic estimate in successive iterative steps to quickly simulate random effects and model parameters. Due to MONOLIX's absence of additional algorithms, users may need to look into additional programs when further modeling techniques are required. Its usefulness and adoption are increased by MONOLIX's user-friendly interface and free availability to academic institutions & regulatory agencies.[48-49]

Phoenix® NLME™-

A wide range of nonlinear mixed-effects modeling algorithms (FO, extended least squares FOCEI, adaptive Gaussian quadrature/Laplacian for Gaussian and non-Gaussian responses, Lindström-Bates FOCE, and a nonparametric engine) and alternative population-based pharmacokinetic modeling algorithms (iterative two-stage, naı¨ve pooled for Gaussian and non-Gaussian responses) are available in Phoenix~ NLME~ (version 1.1), A proprietary program that took the place of Pharsight Corporation's WinNonMix.

Notably, NONMEM~ and Phoenix~ NLME~ use distinct versions of the FO and FOCE algorithms, which could produce different outcomes. As compared to some other programs, Phoenix ® NLME™- is rather easy to use and understand thanks to its straightforward user interface, visual process, and graphic engines.[50-52]

Recent Advances in Pharmacokinetic–Pharmacodynamic Modeling

Pharmacokinetic–pharmacodynamic (PK–PD) modeling has advanced significantly in the past few decades due to the combination of artificial intelligence, systems biology, and computational techniques. A significant advancement in biologics and nanomedicines is the incorporation of physiologically based pharmacokinetic–pharmacodynamic (PBPK–PD) models, which allows for mechanistic forecasts of drug disposition and target engagement across tissues while taking intricate biological barriers into account (Elsevier, 2023). Through finding new drug-target interactions, improving dosage schedules, and learning patterns from massive datasets, artificial intelligence (AI) and machine intelligence-driven modeling have also become potent tools that improve predicted accuracy (Elsevier, 2023).[53-54]

Model-informed drug development (MIDD) is another revolutionary strategy that lowers development costs and speeds up timelines by using quantitative models to guide clinical trial design, dose selection, and approval decisions. Finally, a systems-level knowledge of drug effects is provided by quantitative systems pharmacology (QSP), which integrates PK–PD concepts with mechanistic models of biological networks to enable the logical design of combination therapies.

All of these advances point to a paradigm shift in drug development toward more effective, individualized, and predictive procedures.[55-58]

Regulatory Perspective in Model-Informed Drug Development (MIDD)

Most recently, a clinical pharmacy and Therapeutics editorial defined model-informed drug development (MIDD) as "the integration of mathematical models for managing knowledge, forecasts & decision-making in the study and development of pharmaceuticals. Model-Inspired Drug Development (MIDD) is acknowledged by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) as a crucial tactic to improve the efficiency and efficacy of the process of developing drugs.[59-60] MIDD techniques may help with a wide range of applications in drug development and regulators assessment, including dose optimization, clinical trial design, and giving evidence for clinical success, according to regulators and industrial researchers. In order to promote the incorporation of statistical and quantitative modeling techniques in regulatory submissions, the FDA initiated the Model-Informed Drug Development Pilot Program in 2018.[61-62] By providing recommendations on the application of population pharmacokinetics and PBPK modeling in regulatory submissions, the EMA also encourages model-based evaluations. For dose selection, extrapolation across populations (such as pediatrics), and bioequivalence explanation, the EMA recommends making use of modeling and simulation. These frameworks seek to facilitate evidence-based decision-making and increase the predictability of therapeutic outcomes.[63-64] Therefore, model-based decision making has emerged as a key component of regulatory submissions. These methods offer quantitative support for the design of clinical trials, the optimization of dosage plans, and the interpretation of therapeutic result variability. Regarding approval, labeling, and post-marketing surveillance, regulatory agencies can make better, more transparent judgments by incorporating verified modeling and simulation frameworks. The advantages that pharmaceutical companies gain from taking part in the MID Pilot Program are detailed in a recent industry viewpoint that was published in this publication.[65]

Future Directions

Pharmacokinetic–pharmacodynamic (PK–PD) modeling's future depends on how well it integrates with new data sources and technology to improve accuracy and predictive power in drug development.Model-informed drug development (MIDD) is the process of using quantitative models derived from preclinical and clinical data to make decisions about a medicine's benefit-risk analysis.The effective use of these quantitative models can improve the design and efficacy of clinical trials and, in the end, result in the best dosage for each patient, including those from underrepresented groups.

Personalized Dosing Using PK–PD Models

In integrating unique patient attributes like genetics, age, illness state, and comorbidities into model frameworks, advances in PK–PD modeling are opening the door to personalized or precision medicine. The customized models can optimize dosage schedules to maximize the therapeutic impact and minimize side effects, particularly in high-variability groups including children, the elderly, and patients with liver or kidney disease.

Integration with Real-World Data (RWD)

In controlled clinical trial settings, a more comprehensive understanding of medication performance is possible through the integration of real-world data, such as wearable sensor data, electronic health records, and registries. Post-marketing surveillance and adaptive trial design are supported by the dynamic assessment of drug efficacy, safety, and adherence

in a variety of patient populations made possible by the integration of RWD with PK–PD and physiologically based pharmacokinetic (PBPK) models.

Predictive Modeling for Drug–Drug Interactions (DDIs)

Predictive computer models are being used more and more to predict possible drug-drug interactions in the early stages of research, especially PBPK-based simulations. In anticipating changes in exposure and pharmacologic response, these predictive techniques allow for risk minimization prior to clinical evaluation. In besides improving patient safety, this proactive strategy cuts down on the time and expense involved in late-stage clinical failures. In conclusion, PK-PD modeling is poised to become an essential part of model-informed precision treatments through the integration of personalized modeling, real-world data analytics, and predictive simulation technologies.

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