



# Pharmacometrics: The Already-Present Future of Precision Pharmacology

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## Abstract

The use of mathematical modeling to represent, analyze, make predictions or providing information on data obtained in drug research and development has made pharmacometrics an area of great prominence and importance. The main purpose of pharmacometrics is to provide information relevant to the search for efficacy and safety improvements in pharmacotherapy. Regulatory agencies have adopted pharmacometrics analysis to justify their regulatory decisions, making those decisions more efficient. Demand for specialists trained in the field is therefore growing. In this review, we describe the meaning, history, and development of pharmacometrics, analyzing the challenges faced in the training of professionals. Examples of applications in current use, perspectives for the future, and the importance of pharmacometrics for the development and growth of precision pharmacology are also presented.

**Keywords** Pharmacometrics · Modeling · Simulation · Pharmacology · Pharmacotherapy

## Introduction

Pharmacometrics has emerged as a tool important to the field of clinical pharmacology, allowing for the development and application of mathematical and statistical methods in understanding, characterizing, and predicting exposure and response to drugs. This branch of science aims to create models and simulations of biology, pharmacology, disease, and physiology that can describe and quantify interactions between xenobiotics and patients, human or not, considering beneficial and adverse effects [1–7].

The U.S. Food and Drug Administration (FDA) uses pharmacometrics to quantify substances, diseases, and test information with the aim of assisting in the development of new drugs and regulatory decision-making, making those processes more efficient. That is, drug developers and regulators recognize that pharmacometrics approaches are considered innovative and can improve the interpretation of significant amounts of data and predict large-scale processes. Those techniques, also known as data modeling and

simulation (M&S), can be widely applied in drug research and development and in the translational validation of models through the more efficient use of collected clinical data, contributing to decision making about future studies and to the development of study designs with more assertive dose selection [8–18].

In recent years, the application of pharmacometrics has stood out in the FDA's approval process, whether in dose adjustments for special populations (elderly individuals and children, for example) or in specific diseases such as diabetes and kidney disease [19–40] (Table 1).

By minimizing costs and time (which are considered obstacles in conventional clinical studies) and by maximizing the information generated from trials, pharmacometrics has become a powerful ally in drug research and development [41–46]. In addition, the multidisciplinary vision embodied by pharmacometrics constitutes an important resource to integrate knowledge and promote rational decision-making (Fig. 1).

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**Table 1** Examples of studies submitted to the U.S. Food and Drug Administration (FDA) in which pharmacometrics was used

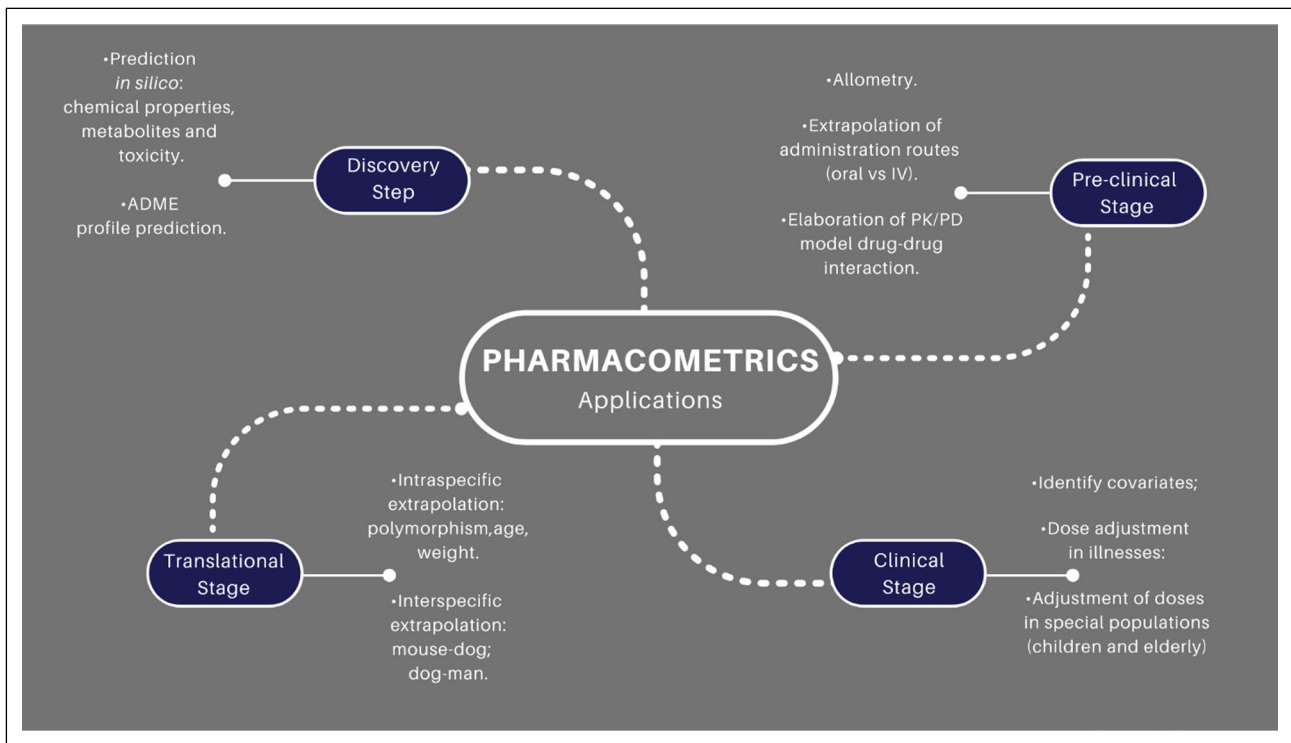
Drug	Pharmacometric objective	Reference
Boceprevir	Dose adjustment in slow metabolizers	[19]
Methylphenidate	Analysis of methylphenidate metabolites in the treatment of attention-deficit hyperactivity disorder	[20]
—	Provision of case studies and updates describing the FDA's efforts in development and application of regulatory science, with a focus on modeling and simulation	[21]
Fingolimod	Evaluation of biomarkers as clinical endpoints, and analysis of the direct relationship between exposure and clinical endpoints	[22]
—	Development of a placebo model for bipolar disorder to help optimize clinical trial designs for studies targeting manic episodes	[23]
Trastuzumab	Reduction in the bias introduced by exposure risk factors, and assessment of the recommended dose regimen	[24]
Paliperidone	Use data as a basis for recommending a wider dose range	[25]
Efavirenz + rifampicin	Evaluation of a drug–drug interaction study and population pharmacokinetic (popPK) analyses	[26]
Methotrexate	Provision of information for designing future clinical trials for the treatment of rheumatoid arthritis	[27]
—	Development of a consolidated set of guiding principles for reporting popPK analyses based on data from a survey of practitioners, plus discussions between industry, consulting, and regulatory scientists	[28]
Canagliflozin	Highlighting the FDA's quantitative clinical pharmacology analyses that were conducted to support the regulatory decision about dose in patients with renal failure	[29]
Dexamethasone	Characterization of proinflammatory cytokine profiles, bone remodeling biomarkers, and bone mineral density in rats with collagen-induced arthritis	[30]
Inhaled corticosteroids	Characterization of the circadian rhythm observed for forced expiratory volume in 1 s in patients with persistent asthma treated with inhaled corticosteroids	[31]
Esomeprazole vigabatrin	Provision of examples and highlighting the role of modeling and simulation in the development and approval of drugs and biologics in pediatric therapy	[32]
Pasireotide	Highlighting the central role of exposure–response analysis in understanding the suitability and risk/benefit of the proposed starting dose of pasireotide	[33]
Gentamicin	Definition of the dose regimen for gentamicin in patients undergoing hemodialysis	[34]
Esomeprazole	Approval of proton pump inhibitors for childhood gastroesophageal reflux disease (for children 1–17 years of age, extrapolation of efficacy from adults to intravenous esomeprazole was accepted)	[35]
Methylphenidate	Assessment of the exposure–response relationships of changes in blood pressure and heart rate in healthy adults taking methylphenidate	[36]
Pembrolizumab	Description of the pharmacokinetic profile of pembrolizumab	[37]
Methotrexate	Assessment of the relative sensitivity of the 3 binary components to support future dose selection and study design in the treatment of rheumatoid arthritis	[38]
Nivolumab	Development of a proposed method for assessing the causal effect of drug exposure on clinical response	[39]
Nintedanib and pirfenidone	Validation and characterization of previously identified acute exacerbations and baseline predictors	[40]

## History and Development of Pharmacometrics

Regulatory authorities such as the FDA and the European Medicines Agency (EMA) have sets of guidelines that describe the experiments needed to meet regulatory requirements in drug development requirements that include M&S. However, the use of pharmacometrics is recent: the first mentions appear in articles by Lee in 1971 and 1976 [1].

The first pharmacometrics group at the FDA's Center for Drug Evaluation and Research (CDER) was established in 1991. Initially, that group changed the focus of drug development, shifting the emphasis from interpretation of dose–response information to analysis of exposure–response data [47].

In 1994, the FDA published guidelines in *ICH E7—Studies in Support of Special Populations: Geriatrics*, with recommendations that pharmacokinetic screening be performed to gather important information about the safety and



**Fig. 1** Steps in the application of pharmacometrics. ADME absorption, distribution, metabolism, excretion, IV intravenous, PK pharmacokinetics, PD pharmacodynamics

efficacy of medications used in elderly individuals. In 1999, the agency issued guidelines on population analyses for the pharmaceutical industry and, in 2003, on exposure–response relationship analyses.

In general, those documents recommended the use of special methods for data collection and analysis, indicating the trend toward the use of Pharmacometrics analyses in the near future.

## Challenges in Teaching Pharmacometrics

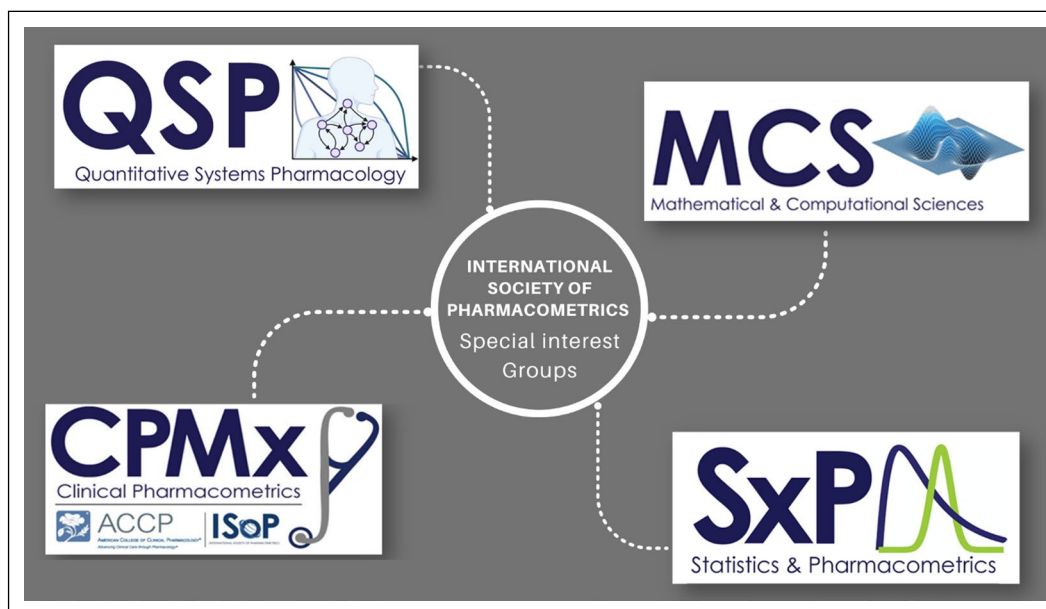
Because Pharmacometrics analyses are considered more efficient than those using conventional methods, the application of Pharmacometrics techniques and the demand for qualified professionals are both increasing exponentially.

On the other hand, obtaining specific training in the field of pharmacometrics led to certain problems being encountered, such as a lack of degree granting in the area and lack of standardization of a basic curriculum. Universities, pharmaceutical industry research centers, the FDA, and nonprofit associations offered only training fellowship programs. An example is the International Society of Pharmacometrics, which emerged in 2013 and which aims to promote and expand the science of pharmacometrics through the integration of multidisciplinary data and continuous innovation

in methods and technologies, leading to impacts on discovery, research, development, and approval and use of new therapies. It also promotes scientific events, offers training materials, and maintains official journals that disseminate research and news. A community of student members who have organized themselves into special interest groups is dedicated to the study of specific subject areas (Fig. 2):

- Clinical pharmacometrics: applying pharmacometrics to guide patient care
- Mathematical and computational sciences: developing new theories, methods, and computational tools
- Quantitative systems pharmacology: advancing the development and use of safe and effective drugs through the application of quantitative systems pharmacology
- Statistics and pharmacometrics: promoting collaboration between pharmacists and biostatisticians to develop innovative approaches in modeling drug development

Bringing together various subject areas is clearly something intrinsic to pharmacometrics, which facilitates the translation of highly complex biologic processes into a quantitative language, therefore making the discipline an effective communications bridge. But integrating data, proposing model structures, interpreting raw data, extracting the most from publicly available data and information, and



**Fig. 2** International Society of Pharmacometrics special interest groups

predicting the value of data and models are complex tasks. Consequently, the need to provide professionals who are competent in pharmacometrics is urgent.

Education in this area has to be standardized through the development of appropriate curricula (with M&S still being incorporated into the undergraduate course in Pharmacy), increasing the frequency and number of training courses so as to offer continuing education that meets the demands of a growing market.

## Perspectives and Applications of Pharmacometrics

Given the complexity of integrating experimental observations with observations emerging from clinical medicine, M&S has been applied in the preclinical phase, to both in silico studies [48] and studies using animal models [49], and also in the clinical stage for patient follow-up [43, 50, 51]. For any drug, its pharmacokinetic profile (any one or a combination of absorption, distribution, metabolism, and excretion), concentration at the site of action, change in effect related to disease-specific changes, and many other variables make interpretation a real challenge when seeking to identify correlations that contribute to more effective pharmacotherapy.

In this sense, modeling aims to develop a mathematical representation that relates the covariates of a process, disease, or system, and simulation seeks to solve mathematical equations so as to show the variables that can be considered relevant to the process in question. Pharmacometrics-based

analyses include drug models (based on pharmacokinetics or PK), exposure–response models (pharmacokinetics–pharmacodynamics or PK–PD), physiology-based models (PBPK), and clinical trials models (Clinical Trial Simulation or CTS). The choice of approach depends on the pharmacokinetics and pharmacodynamics of the drug [52] and on the clinical objectives and questions to be answered.

For example, population pharmacokinetics models (popPK) can be useful if the aim is to find pharmacokinetic parameters and sources of variability in a given population [53]. It is also possible to associate popPK data with pharmacodynamics data to uncover the relationships between exposure and response to a drug, generating a more robust and accurate understanding of the pharmacologic action of a compound in the body [54]. Those models are considered empirical and describe clinical data based on the analysis of concentration as a function of time (“top down”). However, that approach limits the ability to predict pharmacokinetics for a similar drug or to extrapolate results to different physiologic conditions.

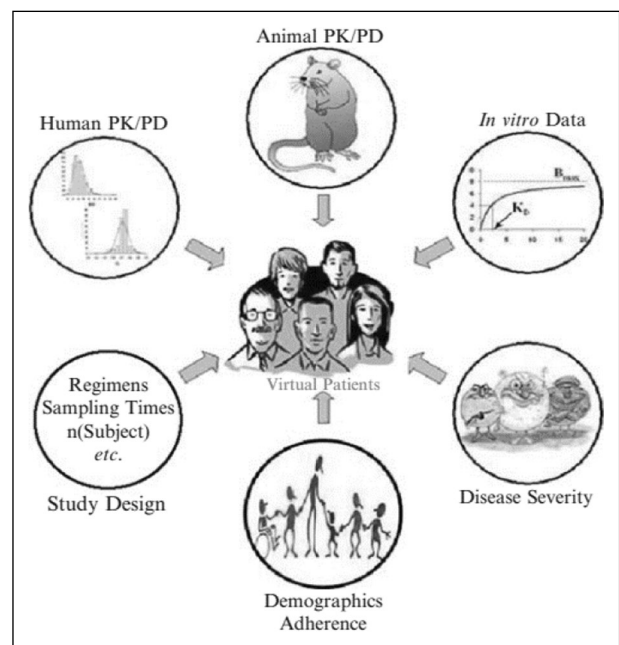
The PBPK models have a mechanistic approach (“bottom up”), compared against which the empirical models are noted to be simpler and more descriptive [55]. But the more complex PBPK models provide more robust prediction with respect to how changes in a pathophysiologic condition can affect specific system parameters leading to changes in pharmacologic effect [54]. Thus, PBPK models consider detailed data about an organism’s physiology (density of receptors, disease progression, homeostatic feedback, blood flow); the drug’s properties (site of action, affinity to target protein, lipophilicity, solubility); and the study design (dose

administered, route and frequency of administration) [56] (Fig. 3). The most common use of PBPK in drug development is the study of drug interactions (60%), followed by studies for pediatric populations (16%) [57].

The growing interest of the pharmaceutical industry in the application of PBPK modeling has increased the number of platforms that integrate this modeling method, among them: Simcyp PBPK Simulator (Certara, Princeton, NJ, U.S.A.; <https://www.certara.com/software/simcyp-pbpk/>), GastroPlus (Simulations Plus, Lancaster, CA, U.S.A.; <https://www.simulations-plus.com/software/gastroplus/>), and PK-Sim (Bayer Technology Services, Leverkusen, Germany; <http://www.systems-biology.com/products/pk-sim.html>).

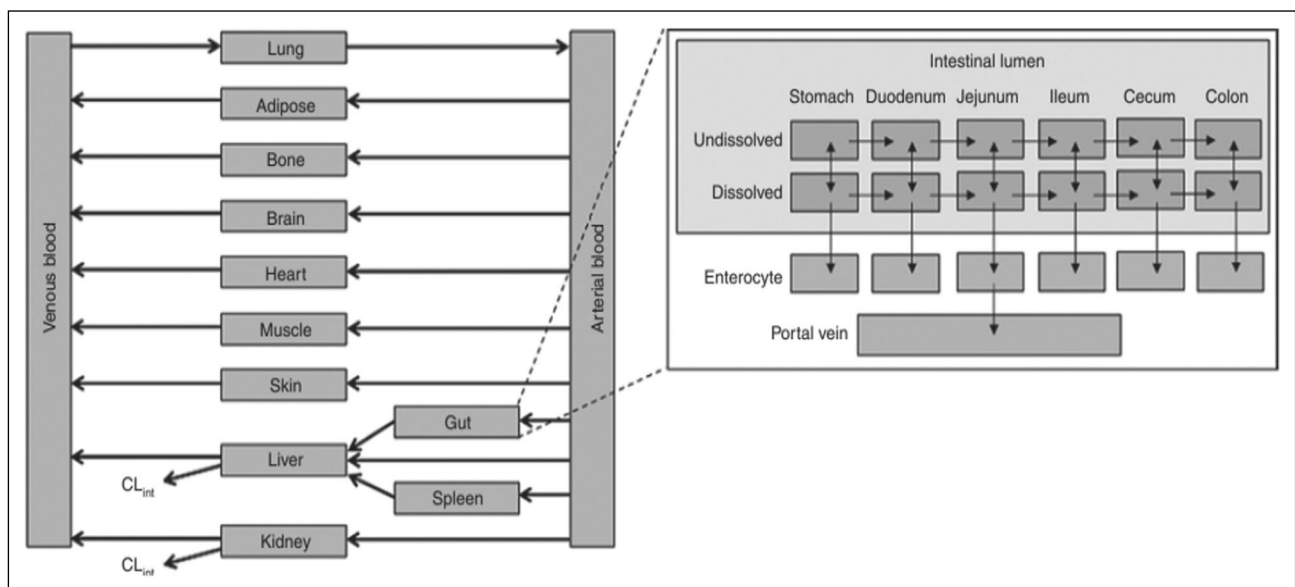
Finally, clinical trial simulation models represent a specialized area of quantitative pharmacology that generates pharmacokinetics or pharmacodynamics profiles (or both) in virtual participants [58] (Fig. 4), considering study design and execution, pathophysiologic changes in participants during the trial, and the pharmacokinetic and pharmacodynamic characteristics of the drug [59].

Pharmacometrics can be used to achieve a variety of objectives, such as analyzing progression in diseases such as HIV-triggered immunodeficiency [60], osteoporosis [61], multiple sclerosis [62], rheumatoid arthritis [63, 64] and diabetes [65–67]. Studies that investigate certain disorders of the central nervous system such as depression, Alzheimer disease, and schizophrenia have increased the use of M&S strategies to assess the efficiency of drugs in preclinical and clinical studies [68].



**Fig. 4** Information sources for a model used in clinical trial simulation. PK/PD pharmacokinetics/pharmacodynamics. (Reprinted from Kimko and Peck, [58])

M&S can also be applied in biomarker follow-up studies [69–71], in the analysis of drug–drug interactions [72–77], for dose adjustment in special populations such as pediatrics [78–81] and in studies focused on the veterinary market [82–86]. Examples are presented in the subsections that follow.



**Fig. 3** Schematic of a physiology-based pharmacokinetics (PBPK) model. The inset presents a detailed representation of the intestine.  $CL_{int}$  intrinsic clearance. (Reprinted from Jones and Rowland-Yeo [56])

## HIV-Triggered Immunodeficiency

Approximately 35 million people worldwide are infected with HIV. In drug research and development, pharmacometrics helps in the search for improvements in treatment that could overcome current limitations related to side effects and monitoring of disease progression.

In the 1990s, a model was developed being able to predict the HIV replication process in the plasma of infected individuals—a great achievement for the study of that disease [87]. The calculated value was approximately 12 billion viral particles per day. Subsequently, several studies using M&S proposed the inclusion of covariates that could be important to an understanding of the dynamics of the infection [88–101].

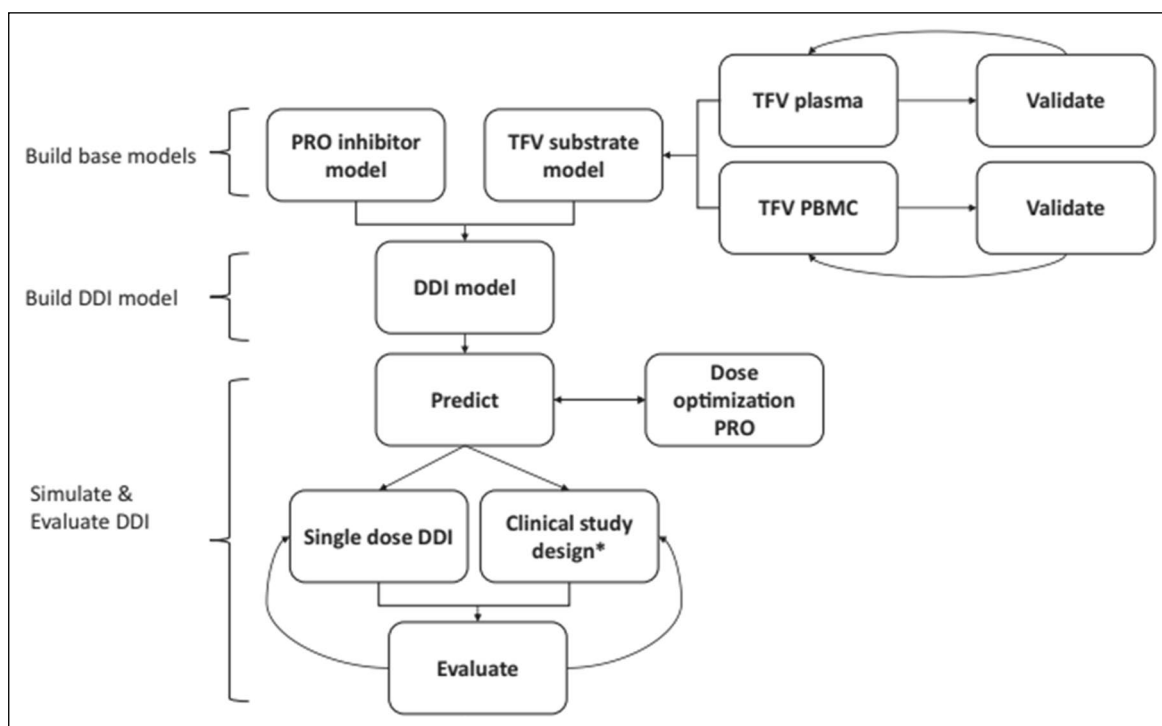
Given the high rate of viral replication observed, mutation and drug resistance must be considered during treatment, and therapy with multiple drugs is necessary. A PBPK model was proposed as a predictive tool for drug–drug interactions with tenofovir [102] (Fig. 5). The model was able to predict a 60% increase in plasma tenofovir exposure and a reduction in renal cell exposure by a factor of 3 after co-administration with 2 g probenecid. The expected increase in exposure, considering the observed clinical pharmacokinetics data, was 15%. The resulting PBPK model can be used to assess the safety and efficacy of drug–drug interactions involving the inhibition of OAT1 and OAT3.

## Osteoporosis

Osteoporosis is a chronic disease characterized by low bone density and tissue deterioration. The result is increased bone fragility and, consequently, greater susceptibility to fractures. A higher incidence is seen in women during menopause. Reduction in estrogenic hormonal activity promotes an imbalance in bone remodeling favoring osteoclast-mediated resorption and less formation of new cells by osteoblasts. M&S has been used to evaluate therapies using various classes of drugs such as bisphosphonates, cathepsin K inhibitors, parathormone and its analogs, and others [103–105].

Bisphosphonates such as etidronate, clodronate, alendronate, and risedronate inhibit bone resorption. After administration, they accumulate rapidly on the bone mineral surface and are released slowly (having half-lives of months to years). The development of PK and PK-PD models for bisphosphonates has traditionally been a challenge because of a lack of assays sufficiently sensitive to quantify the drugs in serum, urine, and bone. This limitation makes it difficult to describe long-term pharmacokinetic parameters and the relationship of exposure with the anti-resorptive effect [106]. Consequently, models linking pathophysiology with clinical biomarkers have gained popularity [61, 107–110].

Such models can be established at various levels of complexity, ranging from descriptive to mechanistic approaches.



**Fig. 5** Proposed drug–drug interactions (DDIs) in a physiology-based pharmacokinetics model workflow. PRO probenecid, TFV tenofovir, PBMC peripheral blood mononuclear cell. (Reprinted from Liu et al. [102])

A drug-trial model was developed for postmenopausal osteoporosis that used a mechanistic approach [111]. The resulting model was able to identify changes in clinically relevant biomarkers over time as a result of disease progression and to assess the response to therapeutic interventions. Models of this kind are of great importance for monitoring and follow-up of patients.

Another class of drugs with anti-resorptive action also had its studies guided by M&S. The inhibitory effects of cathepsin K were compared with those of bisphosphonates. Some cathepsin K inhibitors such as odanacatib are excreted in urine and bile and appear to undergo enterohepatic recirculation, which is reflected by a double peak after oral administration [112]. The pharmacokinetics have been described by several models, in most cases using simple 1-, 2-, or 3-compartment models [113, 114].

The relationship between the serum concentrations of 3 different cathepsin K inhibitors [odanacatib (MK-0822), MK-0674, and MK-1256] and the associated effects on bone resorption markers in various animals and in humans was explored [115]. A better relationship was observed between the unbound drug concentration and anti-resorptive action than between the total drug concentration and anti-resorptive action. The elucidation of such pharmacokinetic–pharmacodynamic relationships will be of great translational value for prediction among various species.

## Diabetes Mellitus

Pharmacometrics is also being used in studies of metabolic diseases. Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia resulting from problems with insulin secretion (type 1, failure to produce insulin), insulin action (type 2, insulin resistance), or both.

Treatment of type 1 diabetes is limited to insulin injections, whereas in type 2 diabetes, patients can control blood glucose with diet and regular physical activity. Anti-hyperglycemic medications available on the market belong to various classes and can be prescribed as monotherapy or in combination.

Biomarkers are of great importance for monitoring the progression of the disease and also for evaluating the response to pharmacologic treatment. In type 2 diabetes, glycosylated hemoglobin A1 (HbA1c) provides information about medium- to long-term glycemic control; plasma glucose and serum insulin, both in fasting state, are the biomarkers most responsive to changes in glycemic control in the short term.

A study applied a population pharmacodynamics model of disease progression that integrated HbA1c, fasting plasma glucose, and fasting serum insulin data into a single comprehensive and physiologically significant structure [65]. The

model provided accurate descriptions of the relationship of biomarkers to disease progression and allowed the long-term effects of various treatments using pioglitazone, metformin, and gliclazide on the loss of beta-cell function and insulin sensitivity to be identified. Expanding that model, Gaitond et al. considered the physiologically significant dynamics between the biomarkers fasting plasma glucose, fasting serum insulin, and HbA1c; the inter-individual differences in disease state for patients at baseline and during disease progression; and clinically significant covariate relationships [116].

The proposed model is of great importance for quantitative pharmacology because it can identify the relationships among patient characteristics, drug action, and disease peculiarities in a physiologically significant analysis.

Other studies of marketed hypoglycemic agents can also be performed using data available in the literature, providing information for evaluating drug dose–response relationships. Models developed based on data from the literature [117, 118] are similar to models developed using patient data, except that the variability estimates reflect the variability of each trial performed [117, 119, 120].

## Multiple Sclerosis

Multiple sclerosis is a chronic debilitating disease characterized by repeated episodes of neurologic dysfunction separated by intermittent periods of partial or complete recovery [121].

The effectiveness of treatment is typically assessed using decline in the frequency of relapses and progression of the deficiency (“endpoints”). In an M&S study, pharmacodynamics models used data from 1319 patients who received placebo or cladribine (Trial 25643 [CLARITY, NCT00213135] and Trial 27820 [CLARITY EXT, NCT00641537]) to characterize the time course of the multiple sclerosis endpoints. Disability scale measures were then evaluated as predictors of efficacy outcomes. The resulting models showed a positive correlation between cladribine use and the endpoints, with a lower (or even nonexistent) relapse rate being observed [122]. Such specific and, above all, reliable models allow for comparisons between drugs already in use and those recently discovered, potentially guiding decisions about whether to continue the use of drugs available for commercialization.

A popPK–pharmacodynamics model was developed to establish the quantitative relationship between pharmacokinetics and the relapse rate in patients who used different peginterferon beta-1a therapeutic regimens [123]. Pharmacokinetics were well described by a 1-compartment model, with first-order absorption and linear elimination kinetics. The results, when compared with those from a placebo

group and with the different regimens, demonstrated that administration every 2 weeks was sufficient for observation of benefit. The study was of great importance in safely proposing a dose adjustment to regulatory agencies.

### Special Populations: Pediatrics

Current EMA and FDA guidelines recommend that dose selection for pediatric studies be based on all available prior information, starting with learnings from adult populations [124, 125]. However, incomplete understandings of the effects of growth and development (or maturation) on drug disposition (pharmacokinetics) and drug effects (pharmacodynamics) remain a significant challenge in defining appropriate doses for children [126].

Advances in quantitative pharmacology and in model-based drug research and development go hand in hand in pediatric research [127, 128]. Pharmacometrics studies for pediatric populations use data from drugs that are already available on the market, but for which information about safety and efficacy for young patients is lacking. The definition of “dose” must consider the clearance, volume of distribution, and dose–response relationship in addition to ontogenic and clinical factors.

Comparative analysis were presented of the various types of models that were used to approve the use of some drugs in pediatrics [129]. Dose selection for esomeprazole was based on pharmacokinetic correspondence with the adult dose, using a simulation based on pharmacokinetics/pharmacodynamics. Adalimumab has been recommended for the treatment of Crohn disease in children based on pharmacokinetic data, the pharmacokinetics/pharmacodynamics ratio, and efficacy and safety data. On the other hand, dose–response for vigabatrin was found to be similar for children and adults, allowing for application of the allometric scale to calculate the pediatric dose.

With PBPK models, a consideration of the effects of the child’s growth and development is possible. Aspects such as body size and composition, tissue blood flow, and

biochemical characteristics (enzyme and transporter profiles) can therefore be included in the M&S. Table 2 shows some examples of the application of this physiology-based approach [130–134].

M&S in pediatric drug research and development can also be used to compare and optimize studies, understand the ontogeny and natural history of disease, and describe pharmacokinetics and pharmacodynamics profiles in clinical pharmacology quantification studies.

### Applications in the Veterinary Market

The animal health industry is on a growth trajectory, fueled by an increase in the number of pets and also by an increased global population that seeks food products such as meat and dairy. In 2014, developers and manufacturers of drugs and vaccines for pets and farm animals achieved a sales record of US\$24 billion, and projections through 2020 reached US\$33 billion [135].

Some differences between the human and veterinary pharmaceutical market are evident. According to the FDA, the cost to develop a new veterinary drug is approximately \$100 million over a period of 7–10 years; for humans, the cost reaches \$1 billion over a period of 12 years. In another comparison, veterinary drug studies are carried out in models of the species of interest, which shortens the pre-clinical phase. Moreover, “animal patients” have a shorter life expectancy, which is also reflected in studies seeking data about efficacy and safety.

The regulatory agencies, the FDA and the EMA, maintain requirements for approved drugs that include proof of manufacturing quality, plus safety and effectiveness. They also require tests to ensure that the tissues and milk of treated animals are safe for human consumption. Given those requirements, pharmacometrics models are also incorporated into the professional routine for the veterinary market. A food safety analysis study used PBPK modeling to predict penicillin concentrations in milk. A high number of animals with residues above the limit was observed because of use

**Table 2** Applications of physiology-based pharmacokinetics models in pediatrics

Drug	Application of the model	Reference
Clobazam	Prediction of drug–drug interactions between clobazam and stiripentol	[130]
Methotrexate	Simulation of the concentration/time profile	[131]
Lorazepam	Simulation of the concentration/time profile and prediction of dose/age based on simulation results	[132]
Acetaminophen	Simulation of concentration/time profile and prediction of pharmacokinetic parameters ( $C_{max}$ , AUC, CL) and urine metabolite profile	[133]
Midazolam, theophylline, omeprazole	Prediction of clearance	[134]

$C_{max}$  peak serum concentration, AUC area under the curve, CL clearance



of a higher than established drug dose. The model was able to quantify penicillin residues in tissue and milk based on a comparison with data from earlier pharmacokinetics studies [136].

Mavacoxib (a COX-2 inhibitor) is approved for the treatment of osteoarthritis in dogs. Simulations based on PopPK modeling in a comparative study using 1317 samples from 286 dogs that received 2 different mavacoxib doses (4 mg/kg and 2 mg/kg) indicated that most dogs (> 85%) treated with mavacoxib 2 mg/kg sustained concentrations above the efficacy level (0.4 µg/mL) throughout the entire dose interval [137]. That study helped to justify reducing the dose of mavacoxib to 2 mg/kg from 4 mg/kg, increasing its therapeutic index.

The use of monoclonal antibody therapies is relatively new in veterinary medicine. The first such antibody was lokivetmab (Cytoint: Zoetis Services, Parsippany, NJ, U.S.A.), which was approved in 2016. It is indicated for the treatment of canine atopic dermatitis, with an anti-IL-31 mechanism of action. A pharmacokinetics/pharmacodynamics model was used to define the recommended dose of Cytoint [138]. Other studies applying M&S to the use of monoclonal antibodies can be found [139, 140], reinforcing the importance of those techniques for precision pharmacology.

Starting from the initial stages of veterinary drug projects, pharmacometrics remains present through to the approval and post-marketing phases, where it assists in responding to regulatory issues. It therefore constitutes an important tool for the veterinary market during its current expansion.

## The Already-Present Future of Precision Pharmacology

Clinical pharmacology is fundamental to the management of drug-related problems and an important instrument of precision medicine. Through its mathematical models (pharmacokinetics, pharmacokinetics/pharmacodynamics, and PBPK), pharmacometrics refines data extrapolation, lending additional confidence to quantitative prediction by integrating modern concepts of the pathophysiology and pharmacology of systems [141, 142].

Pharmacometrics approaches yield strategies for research and development of new drugs and add efficiency and rigor to regulatory processes. This is because the models developed allow us to understand and predict: the physiological phenomena, the action of the studied drug and the results of clinical trials. M&S also reduces costs and time for research and development as it contributes to the choice of a molecule, guides decisions on which way to go, optimizes pre-clinical and clinical planning, assists in dose selection as well as regulatory approvals. Thus, by exploring the

variability and better understanding the molecules, pharmacometrics tools can further support decisions, increasing the probability of successful clinical development and, consequently, the efficacy and safety of new drugs [143].

Studies in Pharmacokinetics, including Pharmacometrics, are essential to understand all these important aspects in the development of new drugs and require a rational approach with a multidisciplinary scope. Only in this way will it be possible to propose innovative strategies in the search for effective and safe pharmacotherapy that will guarantee adherence to treatment and, above all, a positive impact on the patient's quality of life.

For those criteria to be met, furthering the training of professionals to work at the academic level and in the pharmaceutical industry in researching new drugs is essential into the future. In the absence of a specific and standardized curriculum, a constant search for partnerships with clinical research centers and the private sector is necessary to carry out new projects and collaborations, to disseminate expertise, and to deliver services. Only with such collaborations will it be possible to guarantee the already-present future of precision pharmacology.

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## Author Contributions

LCB: Conceptualization, Data curation, Writing—original draft, review and editing; LP Co-supervision, Writing—review and editing; CMC: Writing—review and editing, Supervision, Funding acquisition, Project administration, Resources.

## Declarations

## Conflict of interest

Authors state no conflict of interest.

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