

Interspecies Scaling in Pharmacokinetics: A Novel Whole-Body Physiologically Based Modeling Framework to Discover Drug Biodistribution Mechanisms *In Vivo*

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ABSTRACT: Drug approval processes require extensive testing and have recently put more emphasis on understanding mechanistic drug action in the body including toxicity and safety.¹ Consequently, there is an urgent need in the pharmaceutical industry to develop mechanistic pharmacokinetic (PK) models able to both expedite knowledge gain from experimental trials and, simultaneously, address safety concerns. We previously developed a first principles based whole-body PK model, which incorporated physiological dimensions and drug mass transport. In this follow-up article, we demonstrate how the first principles model in combination with novel physiological scaling laws yields more reliable interspecies and intraspecies extrapolation of drug biodistribution. We show how experimental dose–response data in rats for immunosuppressant cyclosporin are sufficient for predicting the biodistribution of this drug in pigs, monkeys, and humans. The predicted drug concentrations extrapolated by interspecies scaling laws match well with the experimental measurements. These promising results demonstrate that the whole-body PK modeling approach not only elucidates drug mechanisms from a biochemical standpoint, but offers better scaling precision. Better models can substantially accelerate the introduction of drug leads to clinical trials and eventually to the market by offering more understanding of the drug mechanisms, aiding in therapy design, and serving as an accurate dosing tool. © 2011 Wiley Periodical, Inc. and the American Pharmacists Association *J Pharm Sci* 101:1221–1241, 2012

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INTRODUCTION

In drug development, the pharmacology of novel drugs is unknown to a great degree and must be determined by experiments, which, in turn, require mechanistic interpretation through mathematical models. In clinical first-in-human trials, the determination of pharmacokinetics (PK) and pharmacodynamics of novel drugs is critical. The US Food and Drug Administration recommends that human clinical tests be preceded by at least one preclinical trial on laboratory animal species, providing substantial evidence for efficacy and tolerable toxicology risk of the lead. Often, however, crude experimental data about possible

side effects and the drug action mechanism acquired from these animal trials cannot be fully exploited with classical PK models in order to minimize the risks in phase 0, I, and II trials. This article discusses better methods for the prediction of drug biodistribution in humans by extrapolating from smaller laboratory animals by using mechanistic PK models.

From Classical to Mechanistic Whole-Body Pharmacokinetic Models

Pharmacokinetic models aim to establish relationships between drug administration, bioaccumulation, and elimination from dose–response measurements *in vivo*. Typical PK models fit parametric functions with multiple adjustable constants or exponential coefficients.^{2–4} Nonmechanistic parameters such as volume of distribution, area under the curve (AUC), and intrinsic clearance rates are usually computed.

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These classical PK models derive little information about drug reaction kinetics and biotransport phenomena; they also do not satisfy conservation laws, so that drug species balances are not necessarily closed. There is a critical need in the pharmaceutical industry for methods that link modeling, simulation, drug approval, and rigorous experimental data analysis.⁵ Several authors have therefore proposed whole-body physiologically based pharmacokinetic (PBPK) prediction and modeling techniques.^{6–9} PBPK models include several biological subsystems such as blood, the lymphatic and the central nervous system, tissues, and organs, which can further be subdivided into multiple phases including cells and interstitial fluid. PBPK models are accepted as a recommended approach for interspecies and intraspecies extrapolations and to simulate PK profiles for various administration modes and dose regimes. These models incorporate data from many sources such as biochemical, physiological, and drug-dependant parameters for various species, individuals, or with pathological changes.¹⁰ In the literature, compartmental PBPK models are typically stipulated as a set of interconnected vessels with ideal mixing, where both biochemical and transport mechanisms are given as black-box, empirical relations. The kinetics of novel drugs can be studied more systematically with *mechanistic biochemical models in entire organisms*. Several authors have recently used first principles modeling to elucidate the biochemical reaction mechanisms of new drugs *in vivo*.^{10–17} Their model topology does not account for the physiologically consistent blood or lymph perfusion in the arteries, capillaries, and veins of individual organs. Consequently, simulation of blood sampling techniques is imprecise, involving significant errors of PK parameter estimates. These errors limit the fidelity of previous PBPK models for the extrapolation of information from small animals to larger ones, from animals to humans, or for the prediction of drug fate for varying dosing regimes.

Mechanistic PBPK Models with Empirical Scaling Laws

Traditional *interspecies scaling laws* in PK often deploy simple polynomial relationships between properties of interest such as the intrinsic clearance. The *allometric approach* is empirical and rests on the assumption that the underlying physiological processes such as cardiac output, heartbeat frequency, breath duration are only related to the body mass.¹⁸ Typical empirical relations for interspecies scaling include clearance versus body weight, the product of clearance and maximum life-span potential versus body weight, the product of clearance and brain weight versus body weight, and the application of a fixed exponent to clearance.¹⁹ Interesting research from West et al.^{20,21} about allometric scaling laws in biology shows early attempts to incorporate first principles

into determining whole-organism metabolic rates in different animals. In particular, West's group developed a model to explain the origin of quarter-power scaling laws and their use in determining metabolic rates when organism body sizes vary over large orders of magnitude.^{20,21} Another concept, *interspecies scaling* with invariant PK time, results in the removal of the differences in concentration–time profiles due to chronological time.²² Unfortunately, interspecies extrapolation with these simple scaling laws is not satisfactory because it does not account for fundamental biochemical mechanisms, but merely incorporates weight or size factors. Because of the limitation in predictive capabilities, expensive and time-consuming dose–response data have to be acquired in extensive animal trials in rats, then dogs and monkeys, until finally arriving at reasonably safe specifications for human trials.

Multiscale Mechanistic PBPK Model with Mechanistic Intraspecies and Interspecies Scaling

We propose a multiscale biological system model to describe the drug fate in cells, tissues, organs, whole body, among individual subjects, and across species. These variables may be scaled according to fundamental chemical and physical principles to create a consistent and rigorous PK model with better predictive capabilities than classical black-box PK. Specifically, we propose the following first principles interspecies scaling laws:

- (i) Drug fate in cells is determined by selected biochemical reactions. For instance, metabolic activity is observed in hepatocytes or specialized renal cells. These reactions will be scaled according to chemical principles that have to be studied independently, for example, in cell cultures.
- (ii) Drug action in tissues is characterized by biotransport phenomena, such as the mass transfer between blood and interstitial fluid. These mechanisms are generally strong functions of the size of mass transfer area, whereas the specific mass transfer rate of the blood–organ interface may be constant. This category of parameters may be scaled independently to account for the differences in organ surfaces/mass transfer surfaces/specificity of active transport.
- (iii) Biodistribution in organs is determined by physiological and anatomical parameters, blood perfusion rate, and age. Physiological and biodistribution parameters must be determined experimentally. Whole-body drug biodistribution is given by initial conditions of the biological system, such as the drug administration regime or systemic pathology.

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