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SCIENTIFIC BULLETIN

# First-In-Human Trials:

## Considerations for Estimating the Initial Dose

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## Estimating the Initial Dose

The selection of the starting dose for a First-In-Human (FIH) clinical study is tightly controlled and regulated by government agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The purpose of this control is to ensure subject safety and provide oversight across multiple compounds in development by pharmaceutical and biotechnology companies. Both the FDA and EMA have published guidance documents on the selection of starting doses for FIH studies, and both guidance documents state that subject safety and avoidance of toxicity are the primary considerations in any selection algorithm. In effect, the guidance documents work together to provide a single methodology for selection of the starting dose. The FDA guidance document provides a specific algorithm to calculate the maximum recommended starting dose (MRSD) based on toxicology information for the administered doses. The EMA guidance document references the FDA algorithm and then expands the evaluation to consider the minimum anticipated biological effect level (MABEL). After calculating MABEL, the lower dose of the two methods (MABEL and MRSD) is used for the first dose in humans. MABEL is designed to account for new molecular entities with high biological potency and low animal toxicity. Both guidance documents outline the potential use of pharmacokinetic (PK) and pharmacodynamic (PD) information.

### FIH Dose Estimation

Historically, the most widely used method for FIH dose estimation is based on the no observable adverse effect levels (NOAELs) from toxicology studies in multiple species. NOAEL doses are determined in relevant animal studies and normalized to body surface area (in milligrams per square meter), and then extrapolated to human equivalent doses (HEDs). The HED from the most appropriate species is then divided by a safety factor to generate the MRSD in humans. The NOAEL-based approach relies only on administered doses and on a somewhat arbitrary safety factor to estimate the starting dose. While these methods can be conservative, they ignore PK data that can further inform the selection of the starting dose. These empirical approaches can be enhanced with additional analysis of non-clinical data.

In July 2005, the US FDA issued the "Guidance on Estimating the Maximum Recommended Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers". The suggested process for selecting MRSD involves the following: (1) Determine the NOAEL in each animal species tested, (2) Convert the NOAEL to an HED using appropriate scaling factors, (3) Apply a safety factor to the HED to define the human MRSD. For mice, rats, and dogs, HED scaling based on body weight rather than surface area will increase the HED by 12, 6, and 2 times, respectively.

The near-fatal TeGenero (TGN1412) incident led to the introduction of MABEL by the European Medicines Agency (EMA), which issued a guideline in 2007 containing strategies to identify and mitigate risks in FIH trials with investigational medicinal products. The MABEL is the lowest dose that is associated with any biological effect, whether it be toxicity or a desired pharmacological effect. The TGN1412 incident was related to exaggerated pharmacology in humans rather than incorrect calculation of a starting dose recommended by toxicology data: The MRSD was much greater than the minimum biological effect of the compound in humans. The MABEL was introduced to verify that the starting dose is at or below a level that might elicit any pharmacologic effect in humans. MABEL is calculated using the following PK/PD data: (1) in vitro target binding and receptor occupancy in target human and animal cells, (2) in vitro concentration–response curves in target human and animal cells, (3) in vivo dose–exposure–response profiles in relevant animal species, and (4) exposures at pharmacological active doses in relevant animal species.

Advances in PK and PK/PD modeling and simulation have increased the use of exposure-response tools to guide drug

development. Unlike the empirical estimation methods, model-guided approaches have a mechanistic rationale to understand the effect of physiological variables or disease status on PK parameters. In addition to safety, more accurate predictions of human PKs prior to phase I studies have resulted in significant time savings, ranging from 1 to 6 months, during dose escalations.

## Using PK and PD for First in Human Study Dose Estimations

The current PK/PD paradigm in drug development posits that drug effects are a result of circulating levels of drugs in the body. PD responses (i.e., effects) can then be predicted if the circulating drug levels are known. Further, circulating drug levels for an orally administered drug are a function of four key PK parameters: clearance (CL), volume of distribution (V), bioavailability (F), and absorption rate constant (ka). For accurate estimation of human PK and PD responses, solid estimates of these four PK parameters are required. Over the past few decades, many empirical and physiological approaches have been developed for quantitative prediction of human CL and F. These predictive approaches typically require in vivo preclinical data, in vitro metabolism and disposition data obtained from animal and human tissues, and/or physicochemical parameters of the drug compounds. Each approach has its advantages and disadvantages.

### Prediction of Human Clearance

The interspecies scaling includes simple allometry (SA), allometric scaling of CL of unbound drug, rule of exponents (RoE), allometric scaling of drugs with renal and biliary excretion, allometric scaling after normalization by in vitro CL, multi-exponential allometry, the two term power equation, the fraction of unbound drug ($f_u$) corrected intercept method (FCIM), and the liver blood flow method (LBF). Most interspecies scaling predictions are empirical approaches and based on in vivo animal data. However, additional animal and human in vitro metabolism data have been introduced to allometric scaling to improve the accuracy of prediction.

IVIVE (in vitro/in vivo) predictions are physiologically based approaches. Human metabolic clearance is extrapolated from in vitro metabolism in human liver microsomes, hepatocytes, or human cDNA recombinant CYP450 isoenzymes by using a physiologically based scaling factor (PB-SF). The IVIVE is further improved by incorporating correction factors such as a drug-specific factor (SF) derived from the animal CL, an empirical factor determined by a regression between human in vivo intrinsic CL ($CL_{int}$, in vivo) and human in vitro intrinsic CL ($CL_{int}$, in vitro) or protein binding in plasma and/or microsomes. For drugs that undergo renal excretion rather than hepatic metabolism, a physiologically based IVIVE approach was developed to predict human renal clearance (CLR) using glomerular filtration rate.

Computational approaches and statistical tools such as multivariate linear regression (MLR), principal component analysis (PCA), partial least squares (PLS), and back-propagation neural and artificial neural network (ANN) can be employed to establish correlations between human CL and animal CL or physiochemical properties of the compounds.

### Prediction of Volume of Distribution

The volume of distribution is a proportionality factor that relates the amount of drug in the body to the concentration of drug measured in a biological fluid, such as plasma. Current methods to predict V include the (1) extrapolation of animal data, (2) physiologically based pharmacokinetic (PBPK) modeling and (3) in silico approaches that employ quantitative structure-pharmacokinetic relationships (QSPR). A variety of physiologic and physiochemical properties affect V such as molecular weight, charge, transporter affinities, and lipophilicity. Often the extrapolation of animal data, particularly from non-human primates, provides reasonable estimates for V.

### Prediction of Bioavailability and Absorption Rate Constant

Various in vitro, in vivo, and in silico computational approaches have been developed to predict human intestinal absorption and oral bioavailability. The in vitro methods include the Caco-2 monolayer permeability assay, the parallel artificial membrane permeability assay (PAMPA) and the immobilized artificial membrane (IAM) chromatographic assay. In silico models are divided into two classes: Quantitative structure–activity relationship (QSAR) models and PBPK.

### Prediction of Human Plasma Concentration-Time Profiles

When predicting the FIH dosing, special attention is paid to the area under concentration-time (AUC) after oral dosing, elimination half-life, and peak-to-trough plasma concentration ratio. This is because an AUC is required to ensure efficacy and safety. Accurate assessment of the drug's maximum concentration ($C_{max}$) and minimum concentration ($C_{min}$) is useful to avoid unwanted toxicity and maintain efficacious concentrations. Hence, early prediction of the concentration-time profiles for humans is of great importance. Currently, several methods have already been used to predict concentration-time profiles in humans based on preclinical data, such as the species-invariant time method (Dedrick plots), the steady-state concentration mean residence time (MRT) method, and the PBPK model.

### Prediction of Pharmacodynamic Effects

To avoid inaccuracy caused by interspecies differences in exposure-response relationships, PK/PD modeling has been utilized to estimate the pharmacologic effect of a FIH dose. The estimation of PD response in humans can be accomplished using a four-step approach. (1) Development of PD models using in vitro and in vivo data to describe the concentration-response relationships; (2) Modification of the PD model to account for interspecies differences; (3) Incorporation of human PK parameters to provide simulated concentration-time profiles; and (4) Integration of the PD and PK models to predict human response. The final model can be used to design dose regimens that exceed a threshold of efficacy (e.g., $EC_{50}$) yet remain below a threshold for adverse effects (e.g., NOAEL).

## Putting it All Together

The science behind selection of a starting dose for FIH clinical studies involves a complex balancing act between subject safety and pharmacologic activity. The integration of PK and PD information into the selection of the FIH starting dose provides advantages over empirical methods resulting in significant time savings and more clinically relevant results from the FIH clinical study. Subsequent bulletins will discuss additional technical details, constraints, and considerations of using PK and PD information in the selection of the FIH starting dose.

## Coming Soon:

- "Technical Aspects of Setting the First-In-Human Dosing"
- "Comparing First-In-Human Dose Setting for Biologics and Small Molecules"

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