Editorial

# Dose Conversion Between Animals and Humans: A Practical Solution

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## ABSTRACT

Selecting the most appropriate first-in-human and pharmacologically active dose for any new drugs or biologicals is a crucial step before starting a clinical trial investigation in adult healthy human subjects. Extrapolation of dose between various rodent and non-rodent animal species is critical for biomedical researchers during initial drug development. The objective of this review is to provide practical guidance on how allometric scaling based on the body surface area normalization can be effectively utilized for dose conversion between various animal species. The standard conversion factors are included to allow dose translation between animals to humans and humans to animals expressed either in mg/kg or mg/m$^2$. The estimation of a safe starting dose is important to ensure the safety and tolerability of humans during phase-I clinical trials.

**Keywords:** Starting dose, Body surface area, Dose translation, Human equivalent dose, Animal equivalent dose, Interspecies dose conversion, Allometric scaling.

## INTRODUCTION

In drug development, accurate dose conversion, and estimation of the maximum recommended starting dose (MRSD) in first-in-human (FIH) clinical studies are critical. To assure the safety of clinical trials, conversion of dose from animals to humans needed consideration of various factors including body surface area (BSA), pharmacological, physiological, and anatomical variables, pharmacokinetic parameters, metabolic functions, receptors, and life span.[1] Apart from general toxicity considerations, body weight, and BSA, can also be used for dose scaling. The dose conversion between different animal species and humans is significant for pharmaceutical scientists to ensure the safety of new chemical entities (NCE) in human volunteers. Meantime, the dose should be selected to achieve phase I clinical trial objectives. Thus, the key considerations for efficient dose prediction lie in understanding how doses should be scaled for size variation and modified for size-independent differences between various animal species. Based on the physico-chemical and biopharmaceutical properties of the drug and its associated risk, diverse methodologies for estimating the starting dose based on observed toxicity at varying dose levels can be employed.

Estimating MRSD for FIH clinical evaluation of candidate drugs in healthy human subjects is crucial for dose optimization.[2] The main objective of the FIH clinical study for a drug is to test its safety and tolerability without demonstrating any life-threatening adverse events. As per the regulatory requirement, toxicokinetic studies in rodent and at least one non-rodent species is essential to validate the evaluation in humans and the design of the FIH investigation for continuing drug development.[3]

The most popular form for dose extrapolation is allometric scaling, which is

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based on normalizing dose-to-BSA.[4] Typically, there are six methods to determine the FIH dose, namely a) dose-by-factor (based on no observed adverse effect level [NOAEL]), b) pharmacokinetically-guided approach, c) minimum anticipated biological effect level (MABEL), d) pharmacokinetic-pharmacodynamic (PK-PD) model, e) similar drug approach and f) microdosing.[2,5] Indeed, it is also suggested that in case different approaches estimate dissimilar values of a safe dose in humans, then the lowest dose should be considered as the MRSD in FIH studies.[6] This review summarizes the principles behind extrapolating doses between animal species and finding FIH doses for phase-I clinical trials.

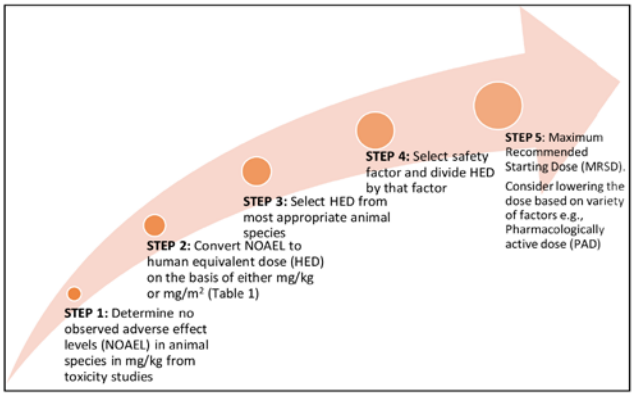


**Figure 1: Schematic representation of five steps to estimate the maximum recommended starting dose administered systematically to human volunteers.**

## DOSE BY FACTOR

The dose by factor is the most frequently used empirical method that utilizes the NOAEL of a drug derived from the dose-response curve of a well-designed preclinical toxicological investigation conducted in the most sensitive animal species to find the MRSD.[7] This method is strictly algorithm-based and focuses more on toxicity than pharmacological aspects. The determination of MSRD for humans is a five steps process wherein preclinical animal toxicity data was used to find NOAEL, scale NOAEL to human equivalent dose (HED), select the most sensitive animal species, divide by safety factor, and consider pharmacologically active dose (PAD)[8] as depicted in Figure 1. A schematic representation of five steps for determining MRSD for FIH trials based on NOAEL is presented in Figure 2. The United States Food and drug administration (USFDA) guidance document explains the algorithm and terminology for obtaining MRSD recommended for initial clinical trial phases in healthy human subjects and subsequent submission of investigational new drug applications. The dose by factor method mainly applies to drugs other than endogenous compounds (e.g., hormones, proteins) generally administered via parenteral and peroral other than topical, and intranasal. To determine the MRSD, complete information on preclinical toxicological data, the PAD, and the pharmacokinetic aspects of the therapeutic are crucial.

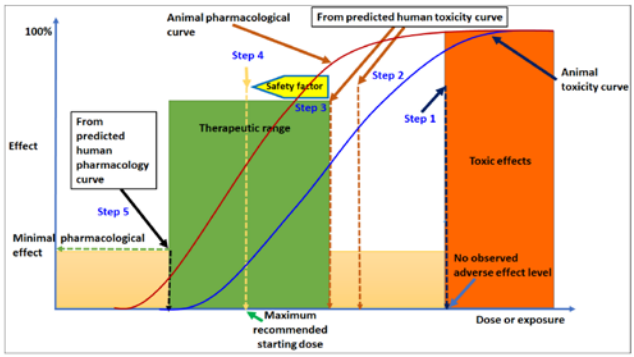


**Figure 2: Schematic representation of five steps for determination of maximum recommended starting dose for first in human trials based on no observed adverse effect.**

### Step 1-NOAEL Determination

The NOAEL in suitable animal species is taken as a reference point for safety to calculate a starting dose of new molecular entities for FIH clinical trials in healthy adult volunteers. It can be defined as the maximum dose that does not initiate adverse events compared to the control animal group in a well-conducted toxicology study. Other non-clinical toxicological evaluation studies indicating apparent toxicity signs and symptoms, variation of enzyme level markers, and drastic changes in pharmacodynamic effects can be likewise utilized for finding NOAEL.

### Step 2- Scale NOAEL to HED

HED is computed based on BSA normalization by applying an allometric scaling exponent of 0.67.[9-10] The surface area (S) of animal species is typically calculated as $S = KW^{0.67}$, where K is constant, and W is the body weight (g) of the animal. The "K" values are determined for different animal species like a mouse (9), rat (9.6), guinea pig (9), rabbit (10), dog (11), cat (8.7), and monkey (11.8). Therefore, for a rabbit weighing 1500 g, the surface area can be computed as $S = 10 \times 1500^{0.67} = 1342.71$ cm$^2$ or 0.1342 m$^2$.

### Step 3- Select the most Sensitive Animal Species

The species that demonstrates the lowest HED or most conservative starting dose is designed as the most sensitive animal species. Nevertheless, if data reveals that a specific species is more apt for examining human toxicity, the HED of that species can be considered.

Before conducting toxicological studies in corresponding species, *in vitro* protein binding and functional evaluation will be more beneficial, particularly for biological drugs.

### Step 4- Divide by Safety Factor

Since most animal species do not assess all potential human toxicities, a safety factor must be incorporated into the HED to guarantee that the starting dose would not lead to undesirable effects in humans. The inclusion of the safety factor assumes that humans are more susceptible to the harmful effects of an active than anticipated from the animal studies besides variation of bioavailability demonstrated among various animal species. The MRSD (mg/kg) used in phase I clinical trials is obtained from HED by dividing with a safety factor of at least 10. However, safety reasons or design limitations reported in animal experiments can escalate the value of the safety factor and consequently decrease the MRSD. The conversion equations and factors included in this document can be also utilized to predict the final dose expressed in mg/m$^2$ (Table 1, Fifth column) instead of the dose expressed in mg/kg.

### Step 5- PAD

The smallest dose evaluated in animals with expected pharmacological effect is termed PAD. The selection of PAD varies between different therapeutic categories and clinical conditions. It is desirable to compare MRSD with PAD obtained from suitable pharmacological models. It is highly recommended to decrease the human starting dose if the pharmacologic HED is less than MRSD due to practical reasons or scientific understanding. In addition, PAD is considered a more sensitive indicator for potential toxicity for a few categories of biological products than NOAEL and, therefore, suggests reducing the MRSD.

### HED calculation based on BSA

Once the NOAEL was determined in the most suitable animal species, it is converted to HED (mg/kg). Thus, NOAEL (mg/kg) can be converted to HED (mg/kg) based on the allometric exponent, which adjusts for differences in BSA between the animal species contributed by significant variation of body weight among animal species. A working weight range of various animal species is shown next to the reference body weight in Table 1. Various studies reported that lethal dose to 10 percent of rodents ($LD_{10}$) and maximum tolerable dose could scale well between various animal species once the doses are normalized to BSA (i.e., mg/m$^2$) using certain animal weight correction factors.[11] For antineoplastic drugs, doses are normalized to BSA using a weight correction factor of $W^{0.75}$ while the remaining drugs' normalization to BSA can be done using the correction factor, $W^{0.67}$.[12-13] The equation to calculate HED is:

$$\text{HED (mg/kg)} = \text{Animal NOAEL (mg/kg)} \times \left(\text{Weight}_{\text{animal}}\ [\text{kg}] / \text{Weight}_{\text{human}}\ [\text{kg}]\right)^{(1-b)} \quad \text{Eq.1}$$

b = 0.75 for interspecies carcinogenicity studies

b = 0.67 for conventional drugs.

Thus, the above equation is modified as below:

$$\text{HED (mg/kg)} = \text{Animal NOAEL (mg/kg)} \times \left(\text{Weight}_{\text{animal}}\ [\text{kg}] / \text{Weight}_{\text{human}}\ [\text{kg}]\right)^{(0.25)} \quad \text{Eq.2}$$

$$\text{HED (mg/kg)} = \text{Animal NOAEL (mg/kg)} \times \left(\text{Weight}_{\text{animal}}\ [\text{kg}] / \text{Weight}_{\text{human}}\ [\text{kg}]\right)^{(0.33)} \quad \text{Eq.3}$$

### Practical example 1

A new antineoplastic candidate drug, the NOAEL value in rats with an average weight of 150 g, is 10 mg/kg. The HED can be calculated using Eq. 2.

$$\text{HED (mg/kg)} = 10 \times (0.15/60)^{0.25} = 2.24 \text{ mg/kg}$$

Therefore, the dose calculated for a 60 kg human is 134.16 mg. For safety reasons, the starting dose for clinical studies is suggested as 13.4 mg/human, calculated by dividing the estimated dose with a safety factor of 10.

### Practical Example 2

A NCE, the NOAEL value in rats with an average weight of 150 g, is 10 mg/kg. HED can be calculated using Eq. 3.

$$\text{HED (mg/kg)} = 10 \times (0.15/60)^{0.33} = 1.38 \text{ mg/kg}$$

Therefore, the dose calculated for a 60 kg human is 83.08 mg. For safety reasons, the starting dose for clinical studies is suggested as 8.31 mg, calculated by dividing the estimated dose by a safety factor of 10.

### Dose conversion between mg/kg to mg/m$^2$

The dose is also linked to body weight even though it cannot be considered the sole factor influencing the dosing approximation. Precise conversion of an mg/kg dose to an mg/m$^2$ dose relies upon the actual weight and surface area of the examined species. A correction factor ($K_m$) is approximated by taking the ratio between

**Table 1: Animal Equivalent Dose (AED) and Human Equivalent Dose (HED) calculation based on Body Surface Area (BSA).**

| Species | Reference body weight (kg) | Working weight range (kg) | Body surface area ($m^2$) | To convert animal dose in mg/kg to HED in mg/$m^2$, multiply by $K_m$ | To convert human dose in mg/kg to AED in mg/kg, multiply human dose by | To convert the human dose in mg/kg to AED in mg/kg, divide the human dose by |
|---|---|---|---|---|---|---|
| | | | | | To convert animal dose in mg/kg to HED in mg/kg, divide the animal dose by | To convert animal dose in mg/kg to HED in mg/kg, multiply the animal dose by |
| **Baboon** | 12 | 7-23 | 0.60 | 20 | 1.8 | 0.541 |
| **Dog** | 10 | 5-17 | 0.50 | 20 | 1.8 | 0.541 |
| **Ferret** | 0.300 | 0.16-0.540 | 0.043 | 7 | 5.3 | 0.189 |
| **Guinea Pig** | 0.400 | 0.208-0.700 | 0.05 | 8 | 4.6 | 0.216 |
| **Hamster** | 0.080 | 0.047-0.157 | 0.016 | 5 | 7.4 | 0.135 |
| **Human** | 60 | - | 1.62 | 37 | - | - |
| **Marmoset** | 0.350 | 0.140-0.720 | 0.06 | 6 | 6.2 | 0.162 |
| **Micro pig** | 12 | 10-33 | 0.74 | 27 | 1.4 | 0.730 |
| **Mini pig** | 40 | 25-64 | 1.14 | 35 | 1.1 | 0.946 |
| **Monkeys** | 3 | 1.4-4.9 | 0.25 | 12 | 3.1 | 0.324 |
| **Mouse** | 0.020 | 0.011-0.034 | 0.007 | 3 | 12.3 | 0.081 |
| **Rabbit** | 1.8 | 0.9-3.0 | 0.15 | 12 | 3.1 | 0.324 |
| **Rat** | 0.150 | 0.080-0.270 | 0.025 | 6 | 6.2 | 0.162 |
| **Squirrel monkey** | 0.600 | 0.290-0.970 | 0.09 | 7 | 5.3 | 0.189 |

the mean weight (kg) of individual animal species to its BSA ($m^2$). Thus, the $K_m$ factor has a unit of $kg/m^2$, which is used for converting mg/kg dose to $mg/m^2$ dose.

$$\frac{mg}{m^2} = K_m \times \frac{mg}{kg} \quad \text{OR} \quad \left(\frac{kg}{m^2} \times \frac{mg}{kg}\right)$$

## Practical Example: Converting mg/kg to mg/m²

To convert an animal or human dose from mg/kg to $mg/m^2$, the dose in mg/kg is multiplied by the conversion factor indicated as $K_m$ (for mass constant) in Table 1 ($5^{th}$ column).

Formula: $mg/kg \times K_m = mg/m^2$

To convert a dose of 30 mg/kg in a dog:
$30\ mg/kg \times 20 = 600\ mg/m^2$

To convert a dose of 2.5 mg/kg in a human:
$2.5\ mg/kg \times 37 = 92.5\ mg/m^2$

## Calculation of $K_m$ Factor

The $K_m$ factor is significant because it is used to convert the dose given in mg/kg to dose in $mg/m^2$ and interspecies dose conversion between HED (mg/kg) to animal equivalent dose (AED) in mg/kg and vice versa. Interspecies dose conversion can be carried out using standard values as displayed in Table 1. This is established on the hypotheses that dose scale well between species or demonstrate a 1:1 relation between species when normalized to BSA. Moreover, the conversion factors can be utilized to provide final dosing units in the $mg/m^2$ form if applicable. For enteral and parenteral administration, HED conversion (mg/kg) is based on BSA normalization. The conversion can be made by either dividing or multiplying with the NOAEL in suitable species by the standard conversion and scaling factors as previously described.

The formula for calculating the $K_m$ factor is;

$$K_m \text{ factor} = \text{Weight in kg/BSA in } m^2$$

## Practical Example

An average rat weighs approximately 0.15 kg (150 g), and the BSA is 0.025 $m^2$.

$$\text{Rat } K_m \text{ factor} = 0.15\ kg/0.025\ m^2 = 6$$

An average human weighs approximately 60 kg, and the BSA is 1.62 $m^2$.

$$\text{Human } K_m \text{ factor} = 60\ kg/1.62\ m^2 = 37$$

As per the USFDA guidance document, the BSA conversion factor, $K_m$, can be calculated using the following two equations: $K_m = 100/K \times W^{0.33}$, where K is a value unique to each species or $K_m = 9.09 \times W^{0.35}$, where a K value unique to each species is not needed. The $K_m$ factor is not a true constant for any animal species but increases within a species as body weight increases. The increase is not linear but increases approximately proportional to $W^{0.67}$. For example, the $K_m$ value in rats varies from 5.2 for a 100 g rat to 7 for a 250 g rat. The $K_m$ value of 6 applies only to rats at the reference weight of 150 g. For standardization and practical purposes, a fixed $K_m$ factor for each species given in Table 1 is preferred.

## Calculation of $K_m$ Ratio

The $K_m$ ratio is calculated by dividing the animal $K_m$ factor by the human $K_m$ factor or vice versa.

$$K_m \text{ ratio}_{(A/H)} = (\text{Animal } K_m / \text{Human } K_m)$$

Or

$$K_m \text{ ratio}_{(H/A)} = (\text{Human } K_m / \text{Animal } K_m)$$

For example, the $K_m$ $\text{ratio}_{A/H}$ (dimensionless number) is calculated as the ratio of the rat/human $K_m$ factor (6/37 = 0.162). Similarly, $K_m$ $\text{ratio}_{H/A}$ can be expressed as the ratio between human and rat $K_m$ factor (37/6 = 6.2).

## Calculation of HED (mg/kg)

To calculate the HED, the animal dose in mg/kg is converted to mg/m$^2$ by multiplying with the $K_m$ factor for that species as described in Table 1 (5$^{th}$ column). Then, the dose in mg/m$^2$ can be changed to HED in mg/kg in humans by dividing by the $K_m$ factor for humans using the formula: (animal dose in mg/kg × animal $K_m$) / human $K_m$ = HED (mg/kg).

## Practical Example

To calculate the HED for a 30 mg/kg dose in dogs with a $K_m$ factor of 20

(30 mg/kg × 20 kg/m$^2$) / 37 kg/m$^2$ = 16.22 mg/kg.

## Calculation of HED (mg/kg) using Table 1

To find the HED values (mg/kg), one can either divide the animal dose (mg/kg) by the $K_m$ $\text{ratio}_{H/A}$ (6$^{th}$ column in Table 1) or multiply the animal dose (mg/kg) with the $K_{m\,A/H}$ ratio (7$^{th}$ column in Table 1) by following the below equations.

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \times K_m \text{ ratio}_{A/H} \quad \text{Eq.5}$$

Or

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} / K_m \text{ ratio}_{H/A} \quad \text{Eq.6}$$

## Practical Example 1

Calculate the HED of an herbal extract that demonstrates a NOAEL value of 60 mg/kg in rats with an average weight of 0.15 kg (150 g).

Apply equation 5:

$$\text{HED (mg/kg)} = 60 \text{ mg/kg} \times 0.162 \; (K_m \text{ ratio}_{(A/H)}) = 9.7 \text{ mg/kg}$$

Or apply equation 6;

$$\text{HED (mg/kg)} = 60 \text{ mg/kg} / 6.2 \; (K_m \text{ ratio}_{(H/A)}) = 9.7 \text{ mg/kg}$$

## Practical Example 2

Calculate the HED of a new compound that exhibits a NOAEL value of 50 mg/kg in rats with an average weight of 0.25 kg (250 g).

Since the average weight of rats is out of the reference size range, a new $K_m$ ratio should be calculated. The $K_m$ value for a 250 g rat is 7. Apply equation 5;

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \times K_m \text{ ratio}_{(A/H)} \; (7/37 = 0.189)$$

$$\text{HED (mg/kg)} = 50 \text{ mg/kg} \times 0.189 \; (K_m \text{ ratio}_{(A/H)}) = 9.45 \text{ mg/kg}$$

It can be also calculated using equation 6;

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} / K_m \text{ ratio}_{(H/A)} \; (37/7 = 5.288)$$

$$\text{HED (mg/kg)} = 50 \text{ mg/kg} / 5.288 \; (K_m \text{ ratio}_{(H/A)}) = 9.45 \text{ mg/kg}$$

If animal weights are outside the working weight range given in Table 1, or for species not included in the Table, an alternative method is utilized for computing the HED. Under these conditions the following formula can be employed:

$$\text{HED} = \text{Animal dose (mg/kg)} \times (\text{Animal weight [kg]} / \text{Human weight [kg]})^{0.33}$$

## Practical example

Consider that a NOAEL of 25 mg/kg was estimated in a study using rabbits weighing 5.0 kg. The 5.0 kg animals

are outside the working range for rabbits of 0.9 to 3.0 kg indicated in Table 1. Use the above equation;

$$HED = 25\ mg/kg \times (5.0/60)^{0.33} = 25 \times 0.44 = 11\ mg/kg$$

### Converting to AED (mg/kg)

The AED can also be calculated based on BSA by either dividing or multiplying the human dose (mg/kg) by the $K_m$ ratio as given in Table 1 or using the following equations;

$$\text{Animal dose (mg/kg)} = \text{HED (mg/kg)} / K_m\ \text{ratio}_{(A/H)} \quad \text{Eq.7}$$

Or

$$\text{Animal dose (mg/kg)} = \text{HED (mg/kg)} \times K_m\ \text{ratio}_{(H/A)} \quad \text{Eq.8}$$

### Practical example

If the HED of a drug is 10 mg/kg, calculate the AED.
Apply equation 7:

$$\text{Animal dose (mg/kg)} = 10\ mg/kg\ /\ 0.162\ (K_m\ \text{ratio}_{(A/H)}) = 62\ mg/kg$$

Or apply equation 8:

$$\text{Animal dose (mg/kg)} = 10\ mg/kg \times 6.2\ (K_m\ \text{ratio}_{(H/A)}) = 62\ mg/kg$$

## PHARMACOKINETICALLY-GUIDED DOSE EXTRAPOLATION

In this approach, the NOAEL and its area under the curve (AUC), indicating the desired systemic drug exposure are evaluated in many animal species to predict the human pharmacokinetic parameters. The most sensitive animal species (index species) that demonstrate the smallest NOAEL and corresponding AUC are determined and subsequently estimated for animal clearance (Cl) value to approximate the Cl in humans using simple allometric scaling. The Cl rate (L/h) is also computed by multiplying the apparent volume of distribution of the drug in liters (L) with the overall elimination rate constant ($h^{-1}$) of the drug. The initial dose is computed as the product of the AUC obtained in the index species and predicted Cl in humans.[2,14] This method expects that only the parent compound is active and demonstrates similar pharmacological activity or toxicity in humans and animals at identical plasma drug concentrations. The major drawback of this method is that it does not consider the interspecies differences due to pharmacodynamics, and dose extrapolation entirely depends on the predictive accuracy of human pharmacokinetic parameters.

### Practical Example

The AUC estimated during the estimation of NOAEL for an investigating therapeutic in rats is 25 $\mu g \cdot h^{-1} \cdot mL\text{-}1$, and the Cl predicted in humans is 10 $L \cdot h^{-1}$. The first dose in humans is computed by the equation:

$$= 25\ mg \cdot h \cdot L^{-1} \times 10\ L \cdot h^{-1} = 250\ mg$$

An appropriate safety factor should be included. Typically, the safety factor incorporated is 10; thus, the starting dose for a clinical trial is 25 mg (per human).

## MABEL

In the MABEL-based approach, *in vitro*, and *in vivo* pharmacological data were used to identify the minimum dose level having relevant activity and subsequently converted to the HED utilizing allometric scaling and a safety factor. This method proposes starting with the lowest dose that is active (likely to cause a MABEL), instead of starting with the greatest dose that is safe. This method works for both biologics and tiny pharmacological compounds, but it necessitates a lot of fundamental data.

## PK-PD MODEL

This method employs mathematical models to approximate a human dose-response relationship while considering the interspecies differences in pharmacokinetics and pharmacodynamics. In this approach, pharmacokinetic and pharmacodynamic evaluation is conducted in animals and key pharmacokinetic parameters such as volume of distribution and Cl are integrated to forecast the dose exposure-response relationship in humans to compute the starting dose. In brief, concentration-effect relationships are established to find the pharmacodynamic parameters such as $EC_{50}$ to develop appropriate pharmacodynamic models. Interspecies differences in concentration-response profiles are identified for therapeutic and adverse effects. Predicted pharmacokinetic parameters are subsequently combined with established pharmacodynamic models to find human dose-response relationships. The major limitation of this approach is the requirement of extensive efforts, time, and cost for the establishment and validation of the proposed PK-PD model.

## SIMILAR-DRUG APPROACH

A similar drug approach is applied, when the drug to be tested belongs to a similar class of drugs with similar pharmacokinetics and pharmacodynamics that are being previously tested in humans.[15] It can be presumed that the amount of the initial dose to NOAEL will be similar for both the drugs and does not expect to produce any toxic events. This method is simple because only limited information is necessary; however, it is restricted to only a few medicines. The main drawback of this method is that it presumes that pharmacokinetic and pharmacodynamic discrepancies between animals and humans are the same for both medications when utilizing a cross-species dosage ratio.

### Practical Example

A new candidate drug B is classified under a similar therapeutic category as drug C, earlier approved for clinical indication in humans. Toxicological studies in rats' most sensitive index species revealed that the NOAEL of drug B is 5 mg/kg/day. The starting dose of drug C was 10 mg/kg/day and the NOAEL of drug C in rats was 4 mg/kg/day.

Based on a similar drug approach:

$$\frac{\text{Starting dose of drug B}}{\text{NOAEL of drug B}} = \frac{\text{Starting dose of drug C}}{\text{NOAEL of drug C}}$$

$$\text{Starting dose of drug B} = \frac{\text{Starting dose of durg C} \times \text{NOAEL of drug B}}{\text{NOAEL of drug C}}$$

$$= \frac{10\ \text{mg/kg/day} \times 5\ \text{mg/kg/day}}{4\ \text{mg/kg/day}} = 125\ \text{mg/kg/day}$$

Therefore, for a 60 kg human the dose will be 750 mg/day. When a safety factor of 10 is used, then the suggested initial dose for the clinical trial should be 75 mg/day.

## MICRO-DOSING

This approach recommends using a higher safety factor, such as $1/100^{th}$ of the dose indicated for pharmacological effect on an mg/m$^2$ basis. It is recommended that the FIH dose calculation takes into account a variety of parameters such as the medicinal molecule's originality, biological efficiency, and mode of action, among others.

## CONCLUSION

This paper covers the basics of dose conversion between species and how to calculate the FIH using allometric scaling. Different approaches to estimating the MRSD of NCEs in adult healthy volunteers are described. The practical consideration recommended in this article based on the USFDA guidelines is useful for computing the upper and lower level of recommended starting doses, and preferably lower human starting dose is more appropriate for clinical trials. Allometric scaling helps scientists interchange doses between species and the various equations provided in this review could be applied. Moreover, the process outlined in this guidance document should promote harmonization among researchers worldwide.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

**AED:** Animal equivalent dose; **BSA:** body surface area; **Cl:** clearance; **FIH:** first in human; **HED:** human equivalent dose; **MRSD:** maximum recommended starting dose; **MABEL:** minimal anticipated biological effect level; **NCE:** new chemical entity; **NOAEL:** no observed adverse effect level; **PAD:** pharmacologically active dose; **PK-PD:** pharmacokinetic-pharmacodynamic; **USFDA:** United States Food and drug administration.

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