# A Guide for Estimating the Maximum Safe Starting Dose and Conversion it between Animals and Humans

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## ABSTRACT

With the development of drugs and the emergence of new drugs, new experiences in animals or clinical trials in humans are important in understanding the translation of the drug dose between different species, as well as converting the dose from animal studies to human or vice versa based on the differences in the average body weight (kg) of species to its body surface area (m<sup>2</sup>) according Allometric approach during extrapolation doses of starting therapeutic agents among the species, this article have provided basic information about estimating the starting dose for clinical trials, especially for phase I and phase II, or about the translation of doses between species using the allometric calling also, based on human equivalent dose we provided method for calculation of injection volume of parenteral formulation.

## **INTRODUCTION**

Effective pharmacological doses and safety are needful for a biological response to occur. Clinical experiments have been conducted on animals and humans to determine the starting dose for different medications due to their importance. It must be emphasized that calculating the dose depends on body weight (mg / kg) is not the correct methodology and this is due to the different physiological and functional systems in the species that lead to a change in the pharmacokinetics of the drug. Also, to increase the effectiveness and safety of clinical trials, the extrapolation and the conversion the dose from an animal to a person depends on the area of surface body, pharmacokinetics, the speed of metabolism, and physiological time. There are four different dosage methods namely dose by factor, pharmacokinetically guided, similar drug, and comparative approaches described in the literature to assess the initial dose (1). The dose by factor depends on the minimal toxicity risk, by using NOAEL knowledge of the drug as defined in animal toxicity studies, to reach a safe starting dose in humans in order to assessment the human equivalent dose (HED) (2). In the pharmacological guided approach, it does not depend on measuring the dose between different drugs, but rather depends on the activity of the drug (3). On the other hand, the similar drug approach depends on the pharmacokinetics, it is expected that the different drugs that are chemically similar will interact in a similar way. Therefore, it is possible to rely on the presence of another drug in the same category for which pharmacokinetic data is available (4). In the case of a comparative approach, to obtain the initial dose the data are studied and compared.

The Allometric Scale is the tool of drug developers use to predict a human (PK) depends on animal data. Prediction methods, such as multidimensional scaling, provide a sneak peek and predict of how the drug might behave in humans before any clinical studies are conducted. It is important to know that the increase in the size of the animal leads to a slowdown in metabolism and a slowing **Keywords:** drug dose conversion, species, body surface area, starting dose, extrapolation.

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of physiological processes, as Allometric scaling is used to describe biochemical, physiological and anatomical changes in animals (5,6,7). Allometric scaling provides necessary information and data for drug developers and regulators (such as the FDA) due to it provides a databased basis for creating a safe starting dose in humans. It depends on between the metabolic rate and the size of the animal's body. The Food and Drug Administration (a federal agency of the United States) based its current guidance on a dose-dependent approach, where the drug (NOAEL) is measured using the effects measure to derive the recommended maximum dose (MRSD) for clinical studies (8). Information needed to estimate (MRSD) includes methods of administration, exposure time, differences in absorption, distribution, metabolism and excretion, animal-to-human extrapolation factors (for example, surface area size factors for body weight) and consideration of the most appropriate types of testing for human induction based on these Factors (9,10, 11). Usually (MRSD) is calculated from preclinical studies of toxicology by applying factor (12). Therefore, the account (MRSD) depends on five steps when entering into human studies.

Step 1, No observed adverse effect level (NOAEL) determination, It is the highest level of dose that does not observed toxic or significant adverse effects comparing with control group.

Step 2, Human equivalent dose (HED) calculation, after setting NOAEL levels in relevant animal studies, they are converted to HED based on body surface area correction factors (i.e.  $W^{0.67}$ ) they must be maintained to choose starting doses for initial studies in healthy adult volunteers.

Step 3, Appropriate animal species selection, Choosing HED to calculate (MRSD) using the most appropriate animal species. Minimal animal species of HED are the most sensitive species and are usually chosen to determine biological risks.

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Step 4, Application of safety factor, it is calculated by dividing HED which calculated from animal NOAEL by the safety factor value is 10.

STEP 5, Consideration of the pharmacologically active dose (PAD), The PAD value that converted in these cases may be a more sensitive indicator of potential toxicity than the NOAEL and might therefore warrant decreasing the MRSD.

The value of the iPad is converted in these cases

#### **Dose calculation**

To determine HED, we use the following equation HED (mg/kg) =Animal NOAEL (mg/kg)

HED (mg/kg) =Animal NOAEL (mg/kg) × (Weight animal (kg)/Weight human (kg)) (1-0.67) (Eq.

1)

The (0.67) It represents the difference in metabolic rate.

**Example 1:** The NOAEL value of new drug in hamster weighing approximately 80g is 13mg/kg. Calculate the starting dose for human studies. Using equation (1): HED (mg/kg) =  $13 \times (0.08/60)^{(1-067)} = 1.46$  mg/kg for a 60 kg human =  $1.46 \times 60 = 87.6$  mg The HED divided by the safety factor of 10. The initial dose in entry into man studies = 87.6/10 = 8.76 mg

The dose also based on the body weight, to the surface area of the body. The correction factor  $(K_m)$  is calculation by:  $K_m = \frac{\text{average of body weight (kg)}}{\text{area of body surface (m2)}}$ (Eq. 2)

Therefore, the  $K_m$  were calculated for different species of animal; table 1 is used to calculate the HED as: HED (mg/kg) = Animal NOAEL (mg/kg)

- × (	Anim	ial I	Km/	/ H1	uma	ın K <sub>m</sub>	) (I	Eq. 3	3)	
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Table 1: Animal Doses converted to Human Equivalent Doses Based on Body Surface Area*							
Species	Reference	Working weight	Body	To convert dose	To convert animal dose in mg/kg		
	body weight	range (kg)	surface	in mg/kg to dose	to HED in mg/ kg, either		
	(kg)		area	in mg/ m²,	Divide animal	Multiply animal	
			(m <sup>2</sup> )	multiply by k <sub>m</sub>	dose by	dose by	
Human	60	-	1.62	37	-	-	
Mouse	0.02	0.011-0.034	0.007	3	12.3	0.081	
Hamster	0.08	0.047-0.167	0.016	5	7.4	0.135	
Rat	0.15	0.08-0.27	0.025	6	6.2	0.162	
Ferret	0.30	0.16-0.54	0.043	7	5.3	0.189	
Guinea pig	0.40	0.208-0.700	0.05	8	4.6	0.216	
Rabbit	1.8	0.90-3.0	0.15	12	3.1	0.324	
Dog	10	5-17	0.50	20	1.8	0.541	
Monkeys	3	1.4-4.9	0.25	12	3.1	0.324	
(rhesus)							
Marmoset	0.35	0.14-0.72	0.06	6	6.2	0.162	
Squirrel	0.60	0.29-0.97	0.09	7	5.3	0.189	
monkey							
Baboon	12	7-23	0.60	20	1.8	0.541	
Micro pig	20	10-33	0.74	27	1.4	0.730	
Mini pig	40	25-64	1.14	35	1.1	0.946	
*Data obtained from Food and Drug Administration draft guidelines [8].							

From Table 1, which was obtained from the Food and Drug Administration (FDA) draft guidelines, the K<sub>m</sub> ratio value obtained by dividing K<sub>m</sub> factor for a human by a K<sub>m</sub> factor for an animal or vice versa, and to facilitate the of calculating the value of the HED by either dividing or multiplying the animal dose with the K<sub>m</sub> ratio values in Table 1. Despite this, the K<sub>m</sub> values change according to the type of animal species and increase proportional to Weight<sup>2/3</sup> (W<sup>2/3</sup>) within an animal species as body weight increase.

If the weight is increase:

 $K_m = K_m$  value for the reference body weight + ( $K_m$  value for the reference body weight ×  $W^{2/3}$ ) (Eq. 4. 1)

If the weight is decrease:

 $K_m = K_m$  value for the reference body weight - ( $K_m$  value for the reference body weight ×  $W^{2/3}$ ) (Eq. 4. 2)

W = weight (kg)

**Example 2:** Calculate the K<sub>m</sub> value for the guinea pigs if you know the weight are 300g, 550g.

The  $k_m$  = 8 for the 400 g Guinea pigs as a reference body weight (kg) in table 1.

For 300 g Guinea pigs: the weight is decrease 100 g (0.1 kg) from the reference body weight

Using equation 4.2

 $K_m = 8 - (8 \times 0.1^{2/3}) = 8 - 1.7 = 6.3$ 

For 550 g Guinea pigs: the weight is increased 150 g (0.15 kg) from the reference body weight.

Using equation 4. 1  $K_m = 8 + (8 \times 0.15^{2/3}) = 8 + 2.2 = 10.2$ 

**Example 3:** Calculate the HED for newly developed drug, the NOAEL value in guinea pig is 70 mg/kg. if the average weight that used of Guinea pigs 400g or the average weight that used of Guinea pigs 550g. Using equation 3:

If use the Guinea pigs (average weight = 400g); the Km = 8 (table 1)

HED (mg/kg) = 70 (mg/kg) ×  $\left(\frac{8}{37}\right)$  = 15.1 mg/kg in human If use the Guinea pigs (average weight = 550g); Km = 10.2 (calculated in the example 2)

HED (mg/kg) = 70 (mg/kg) ×  $(\frac{10.2}{37})$  = 19.29 mg/kg in human

To convert dose in mg/kg to mg/m<sup>2</sup> of humans or animals is carried out using the K<sub>m</sub> factor in table1 as:  $mg/m^2 = K_m \times (mg/kg)$  (Eq. 5) The mg/m2 conversion between species is not supported for drug administered by subcutaneous, intramuscular, topical, or nasal. as well as proteins administered parenterally with molecular weight >100,000 Daltons. In a similar way to calculate of HED, the animal equivalent dose AED can be calculated by depending on the surface area, either by multiplying or by dividing it by the human dose (mg/kg) by the Km in the table 2. Where the AED can be calculated from the following equation.

Table 2: Animal equivalent dose (AED) calculation based on body surface area*							
Species	Reference body	To convert dose	To convert human dose in mg/kg to AED				
	weight (kg)	in mg/kg to dose in	in mg/kg, either				
		mg/m2, divide by	Multiply human	Divide human dose			
		Km	dose by	by			
Human	60	37	-	-			
Mouse	0.02	3	12.3	0.081			
Hamster	0.08	5	7.4	0.135			
Rat	0.15	6	6.2	0.162			
Ferret	0.30	7	5.3	0.189			
Guinea pig	0.40	8	4.6	0.216			
Rabbit	1.8	12	3.1	0.324			
Dog	10	20	1.8	0.541			
Monkeys (rhesus)	3	12	3.1	0.324			
Marmoset	0.35	6	6.2	0.162			
Squirrel monkey	0.60	7	5.3	0.189			
Baboon	12	20	1.8	0.541			
Micro pig	20	27	1.4	0.730			
Mini pig	40	35	1.1	0.946			
*Data adapted and modified from Food and Drug Administration draft guidelines [8]							

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AED (mg/kg) = Human dose (mg/kg)  $\times$  K<sub>m</sub> ratio (Eq. 6)

**Example 4:** The HED for the particular drug is 15 which calculated using the rabbit, calculate the AED.

From equation 6:

AED =  $15 \times 3.1 = \frac{15}{0.324} = 46.5 \text{ mg/kg}.$ 

Finally, the injection volume of parenteral formulation calculated using the following equation.

Injection	volume	(ml)
Animal weight (kg	(Fa 7)	
Concent	ration (mg/ml)	(Eq. 7)

**Example 5:** Calculated the injection volume for hypothesis drug. The concentration of this drug formulation is 33 mg/mL, the AED is 46.5 mg/kg, also the rabbit weight is 1.8 Kg. the drug administrated through intraperitoneal rout.

Using equation 7

Injection volume (ml) =  $\frac{1.8 \text{ (Kg)} \times 46.5 \text{ (mg/Kg)}}{33 \text{ mg/mL}}$  = 2.5 mL in the lower left quadrant.

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## **Conflict of interest**

There are no conflicts of interest.

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