

Contains Nonbinding Recommendations

proteins and limited reactivity in species commonly used for toxicity testing. In such cases, in vitro binding and functional studies should be conducted to select an appropriate, relevant species before toxicity studies are designed (refer to ICH guidance for industry *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* for more details³). (However, if serious toxicities are observed in an animal species considered less relevant, those toxicities should be taken into consideration in determining the species to be used to calculate an HED. For example, in one particular case, dog was selected as the animal species used for calculation of an HED because of unmonitorable cardiac lesions, even though the rat was considered the most relevant species based on pharmacological activity data.) Additionally, a species might be considered an inappropriate toxicity model for a given drug if the dose-limiting toxicity in that species was concluded to be of limited value for human risk assessment, based on historical comparisons of toxicities in the animal species to those in humans across a therapeutic class (i.e., the dose-limiting toxicity is species-specific). In this case, data from that species should not be used to derive the HED. Without any additional information to guide the choice of the most appropriate species for assessing human risk, the most sensitive species is designated the *most appropriate*, because using the lowest HED would generate the most conservative starting dose.

A safety factor should then be applied to the HED to increase assurance that the first dose in humans will not cause adverse effects. The use of the safety factor should be based on the possibility that humans may be more sensitive to the toxic effects of a therapeutic agent than predicted by the animal models, that bioavailability may vary across species, and that the models tested do not evaluate all possible human toxicities. For example, ocular disturbances or pain (e.g., severe headaches) in humans can be significant dose-limiting toxicities that may go undetected in animal studies.

In general, one should consider using a safety factor of at least 10. The MRSD should be obtained by dividing the HED by the safety factor. Safety concerns or design shortcomings noted in animal studies may increase the safety factor, and thus reduce the MRSD further. Alternatively, information about the pharmacologic class (well-characterized classes of therapeutics with extensive human clinical and preclinical experience) may allay concerns and form the basis for reducing the magnitude of the default safety factor and increasing the MRSD. Although a dose lower than the MRSD can be used as the actual starting dose, the process described in this guidance will derive the maximum recommended starting dose. This algorithm generates an MRSD in units of mg/kg, a common method of dosing used in phase 1 trials, but the equations and conversion factors provided in this guidance (Table 1, second column) can be used to generate final dosing units in the mg/m² form if desired.

As previously stated, for purposes of initial clinical trials in adult healthy volunteers, the HED should ordinarily be calculated from the animal NOAEL. If the HED is based on an alternative index of effect, such as the pharmacologically active dose (PAD), this exception should be prominently stipulated in descriptions of starting dose calculations.

³ We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

Contains Nonbinding Recommendations

The remainder of this guidance provides a description of the individual steps in the recommended process and the reasoning behind each step.

IV. STEP 1: NO OBSERVED ADVERSE EFFECT LEVEL DETERMINATION

The first step in determining the MRSD is to review and evaluate the available animal data so that a NOAEL can be determined for each study. Several definitions of NOAEL exist, but for selecting a starting dose, the following is used: the highest dose level that does not produce a significant increase in adverse effects in comparison to the control group. In this context, adverse effects that are biologically significant (even if they are not statistically significant) should be considered in the determination of the NOAEL. The NOAEL is a generally accepted benchmark for safety when derived from appropriate animal studies and can serve as the starting point for determining a reasonably safe starting dose of a new therapeutic in healthy (or asymptomatic) human volunteers.

The NOAEL is not the same as the *no observed effect level (NOEL)*, which refers to any effect, not just an adverse one, although in some cases the two might be identical. The definition of the NOAEL, in contrast to that of the NOEL, reflects the view that some effects observed in the animal may be acceptable pharmacodynamic actions of the therapeutic and may not raise a safety concern. The NOAEL should also not be confused with *lowest observed adverse effect level (LOAEL)* or *maximum tolerated dose (MTD)*. Both of the latter concepts are based on findings of adverse effects and are not generally used as benchmarks for establishing safe starting doses in adult healthy volunteers. (The term *level* refers to dose or dosage, generally expressed as mg/kg or mg/kg/day.)

Initial IND submissions for first-in-human studies by definition lack in vivo human data or formal allometric comparison of pharmacokinetics. Measurements of systemic levels or exposure (i.e., AUC or C_{max}) cannot be employed for setting a safe starting dose in humans, and it is critical to rely on dose and observed toxic response data from adequate and well-conducted toxicology studies. However, there are cases where nonclinical data on bioavailability, metabolite profile, and plasma drug levels associated with toxicity may influence the choice of the NOAEL. One such case is when saturation of drug absorption occurs at a dose that produces no toxicity. In this instance, the lowest saturating dose, not the highest (nontoxic) dose, should be used for calculating the HED.

There are essentially three types of findings in nonclinical toxicology studies that can be used to determine the NOAEL: (1) overt toxicity (e.g., clinical signs, macro- and microscopic lesions); (2) surrogate markers of toxicity (e.g., serum liver enzyme levels); and (3) exaggerated pharmacodynamic effects. Although the nature and extent of adverse effects can vary greatly with different types of therapeutics, and it is anticipated that in many instances, experts will disagree on the characterization of effects as being adverse or not, the use of NOAEL as a benchmark for dose-setting in healthy volunteers should be acceptable to all responsible investigators. As a general rule, an adverse effect observed in nonclinical toxicology studies

Contains Nonbinding Recommendations

used to define a NOAEL for the purpose of dose-setting should be based on an effect that would be unacceptable if produced by the initial dose of a therapeutic in a phase 1 clinical trial conducted in adult healthy volunteers.

V. STEP 2: HUMAN EQUIVALENT DOSE CALCULATION

A. Conversion Based on Body Surface Area

After the NOAELs in the relevant animal studies have been determined, they are converted to HEDs. A decision should be made regarding the most appropriate method for extrapolating the animal dose to the equivalent human dose. Toxic endpoints for therapeutics administered systemically to animals, such as the MTD, are usually assumed to scale well between species when doses are normalized to body surface area (i.e., mg/m²) (EPA 1992; Lowe and Davis 1998). The basis for this assumption lies primarily with the work of Freireich et al. (1966) and Schein et al. (1970). These investigators reported that, for antineoplastic drugs, doses lethal to 10 percent of rodents (LD₁₀s) and MTDs in nonrodents both correlated with the human MTD when the doses were normalized to the same administration schedule and expressed as mg/m². Despite the subsequent analyses showing that the MTDs for this set of drugs scale best between species when doses are normalized to W^{0.75} rather than W^{0.67} (inherent in body surface area normalization) (Travis and White 1988; Watanabe et al. 1992), normalization to body surface area has remained a widespread practice for estimating an HED based on an animal dose.

An analysis of the affect of the allometric exponent on the conversion of an animal dose to the HED was conducted (see Appendix A). Based on this analysis and on the fact that correcting for body surface area increases clinical trial safety by resulting in a more conservative starting dose estimate, it was concluded that the approach of converting NOAEL doses to an HED based on body surface area correction factors (i.e., W^{0.67}) should be maintained for selecting starting doses for initial studies in adult healthy volunteers. Nonetheless, use of a different dose normalization approach, such as directly equating the human dose to the NOAEL in mg/kg, may be appropriate in some circumstances. Deviations from the body surface area approach, when describing the conversion of animal dose to HED, should be justified. The basis for justifying direct mg/kg conversion and examples in which other normalization methods are appropriate are described in the following subsection.

Although normalization to body surface area is an appropriate method for extrapolating doses between species, consistent factors for converting doses from mg/kg to mg/m² have not always been used. Given that body surface area normalization provides a reasonable approach for estimating an HED, the factors used for converting doses for each species should be standardized. Since body surface area varies with W^{0.67}, the conversion factors are dependent on the weight of the animals in the studies. However, analyses conducted to address the effect of body weight on the actual BSA-CF demonstrated that a standard factor provides a reasonable estimate of the HED over a broad range of human and animal weights (see Appendix B). The conversion factors and divisors shown in Table 1 are therefore recommended as the standard

Contains Nonbinding Recommendations

values to be used for interspecies dose conversions for NOAELs. (These factors may also be applied when comparing safety margins for other toxicity endpoints (e.g., reproductive toxicity and carcinogenicity) when other data for comparison (i.e., AUCs) are unavailable or are otherwise inappropriate for comparison.)

Species	To Convert Animal Dose in mg/kg to Dose in mg/m ² , Multiply by k _m	To Convert Animal Dose in mg/kg to HED ^a in mg/kg, Either:	
		Divide Animal Dose By	Multiply Animal Dose By
Human	37	---	---
Child (20 kg) ^b	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys ^c	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

^a Assumes 60 kg human. For species not listed or for weights outside the standard ranges, HED can be calculated from the following formula:

$$\text{HED} = \text{animal dose in mg/kg} \times (\text{animal weight in kg} / \text{human weight in kg})^{0.33}$$

^b This k_m value is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.

^c For example, cynomolgus, rhesus, and stump-tail.

B. Basis for Using mg/kg Conversions

The factors in Table 1 for scaling animal NOAEL to HEDs are based on the assumption that doses scale 1:1 between species when normalized to body surface area. However, there are occasions for which scaling based on body weight (i.e., setting the HED (mg/kg) = NOAEL (mg/kg)) may be more appropriate. To consider mg/kg scaling for a therapeutic, the available data should show that the NOAEL occurs at a similar mg/kg dose across species. The following circumstances should exist before extrapolating to the HED on a mg/kg basis rather than using

Contains Nonbinding Recommendations

the mg/m^2 approach. Note that mg/kg scaling will give a twelve-, six-, and twofold higher HED than the default mg/m^2 approach for mice, rats, and dogs, respectively. If these circumstances do not exist, the mg/m^2 scaling approach for determining the HED should be followed as it will lead to a safer MRSD.

1. NOAELs occur at a similar mg/kg dose across test species (for the studies with a given dosing regimen relevant to the proposed initial clinical trial). (However, it should be noted that similar NOAELs on a mg/kg basis can be obtained across species because of differences in bioavailability alone.)
2. If only two NOAELs from toxicology studies in separate species are available, one of the following should also be true:
 - The therapeutic is administered orally and the dose is limited by local toxicities. Gastrointestinal (GI) compartment weight scales by $W^{0.94}$ (Mordenti 1986). GI volume determines the concentration of the therapeutic in the GI tract. It is then reasonable that the toxicity of the therapeutic would scale by mg/kg ($W^{1.0}$).
 - The toxicity in humans (for a particular class) is dependent on an exposure parameter that is highly correlated across species with dose on a mg/kg basis. For example, complement activation by systemically administered antisense oligonucleotides in humans is believed to be dependent upon C_{max} (Geary et al. 1997). For some antisense drugs, the C_{max} correlates across nonclinical species with mg/kg dose and in such instances mg/kg scaling would be justified.
 - Other pharmacologic and toxicologic endpoints also scale between species by mg/kg for the therapeutic. Examples of such endpoints include the MTD, lowest lethal dose, and the pharmacologically active dose.
 - There is a robust correlation between plasma drug levels (C_{max} and AUC) and dose in mg/kg .

C. Other Exceptions to mg/m^2 Scaling Between Species

Scaling between species based on mg/m^2 is not recommended for the following categories of therapeutics:

1. Therapeutics administered by alternative routes (e.g., topical, intranasal, subcutaneous, intramuscular) for which the dose is limited by local toxicities. Such therapeutics should be normalized to concentration (e.g., mg/area of application) or amount of drug (mg) at the application site.
2. Therapeutics administered into anatomical compartments that have little subsequent distribution outside of the compartment. Examples are intrathecal, intravesical,

Contains Nonbinding Recommendations

intraocular, or intrapleural administration. Such therapeutics should be normalized between species according to the compartmental volumes and concentrations of the therapeutic.

3. Proteins administered intravascularly with $M_r > 100,000$ daltons. Such therapeutics should be normalized to mg/kg.

VI. STEP 3: MOST APPROPRIATE SPECIES SELECTION

After the HEDs have been determined from the NOAELs from all toxicology studies relevant to the proposed human trial, the next step is to pick one HED for subsequent derivation of the MRSD. This HED should be chosen from the most appropriate species. In the absence of data on species relevance, a default position is that the most appropriate species for deriving the MRSD for a trial in adult healthy volunteers is the most sensitive species (i.e., the species in which the lowest HED can be identified).

Factors that could influence the choice of the most appropriate species rather than the default to the most sensitive species include: (1) differences in the absorption, distribution, metabolism, and excretion (ADME) of the therapeutic between the species, and (2) class experience that may indicate a particular animal model is more predictive of human toxicity. Selection of the most appropriate species for certain biological products (e.g., human proteins) involves consideration of various factors unique to these products. Factors such as whether an animal species expresses relevant receptors or epitopes may affect species selection (refer to ICH guidance for industry *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* for more details).

When determining the MRSD for the first dose of a new therapeutic in humans, absorption, distribution, and elimination parameters will not be known for humans. Comparative metabolism data, however, might be available based on in vitro studies. These data are particularly relevant when there are marked differences in both the in vivo metabolite profiles and HEDs in animals. Class experience implies that previous studies have demonstrated that a particular animal model is more appropriate for the assessment of safety for a particular class of therapeutics. For example, in the nonclinical safety assessment of the phosphorothioate antisense drugs, the monkey is considered the most appropriate species because monkeys experience the same dose limiting toxicity as humans (e.g., complement activation) whereas rodents do not. For this class of therapeutics, the MRSD would usually be based on the HED for the NOAEL in monkeys regardless of whether it was lower than that in rodents, unless unique dose limiting toxicities were observed with the new antisense compound in the rodent species.

VII. STEP 4: APPLICATION OF SAFETY FACTOR

Once the HED of the NOAEL in the most appropriate species has been determined, a safety factor should then be applied to provide a margin of safety for protection of human subjects receiving the initial clinical dose. This safety factor allows for variability in extrapolating from

Contains Nonbinding Recommendations

animal toxicity studies to studies in humans resulting from: (1) uncertainties due to enhanced sensitivity to pharmacologic activity in humans versus animals; (2) difficulties in detecting certain toxicities in animals (e.g., headache, myalgias, mental disturbances); (3) differences in receptor densities or affinities; (4) unexpected toxicities; and (5) interspecies differences in ADME of the therapeutic. These differences can be accommodated by lowering the human starting dose from the HED of the selected species NOAEL.

In practice, the MRSD for the clinical trial should be determined by dividing the HED derived from the animal NOAEL by the safety factor. The default safety factor that should normally be used is 10. This is a historically accepted value, but, as described below, should be evaluated based on available information.

A safety factor of 10 may not be appropriate for all cases. The safety factor should be raised when there is reason for increased concern, and lowered when concern is reduced because of available data that provide added assurance of safety. This can be visualized as a sliding scale, balancing findings that mitigate the concern for harm to healthy volunteers with those that suggest greater concern is warranted. The extent of the increase or decrease is largely a matter of judgment, using the available information. It is incumbent on the evaluator to clearly explain the reasoning behind the applied safety factor when it differs from the default value of 10, particularly if it is less than 10.

A. Increasing the Safety Factor

The following considerations indicate a safety concern that might warrant increasing the safety factor. In these circumstances, the MRSD would be calculated by dividing the HED by a safety factor that is greater than 10. If any of the following concerns are defined in review of the nonclinical safety database, an increase in the safety factor may be called for. If multiple concerns are identified, the safety factor should be increased accordingly.

- **Steep dose response curve.** A steep dose response curve for significant toxicities in the most appropriate species or in multiple species may indicate a greater risk to humans.
- **Severe toxicities.** Qualitatively severe toxicities or damage to an organ system (e.g., central nervous system (CNS)) indicate increased risk to humans.
- **Nonmonitorable toxicity.** Nonmonitorable toxicities may include histopathologic changes in animals that are not readily monitored by clinical pathology markers.
- **Toxicities without premonitory signs.** If the onset of significant toxicities is not reliably associated with premonitory signs in animals, it may be difficult to know when toxic doses are approached in human trials.

Contains Nonbinding Recommendations

- **Variable bioavailability.** Widely divergent or poor bioavailability in the several animal species, or poor bioavailability in the test species used to derive the HED, suggest a greater possibility for underestimating the toxicity in humans.
- **Irreversible toxicity.** Irreversible toxicities in animals suggest the possibility of permanent injury in human trial participants.
- **Unexplained mortality.** Mortality that is not predicted by other parameters raises the level of concern.
- **Large variability in doses or plasma drug levels eliciting effect.** When doses or exposure levels that produce a toxic effect differ greatly across species or among individual animals of a species, the ability to predict a toxic dose in humans is reduced and a greater safety factor may be needed.
- **Nonlinear pharmacokinetics.** When plasma drug levels do not increase in a dose-related manner, the ability to predict toxicity in humans in relation to dose is reduced and a greater safety factor may be needed.
- **Inadequate dose-response data.** Poor study design (e.g., few dose levels, wide dosing intervals) or large differences in responses among animals within dosing groups may make it difficult to characterize the dose-response curve.
- **Novel therapeutic targets.** Therapeutic targets that have not been previously clinically evaluated may increase the uncertainty of relying on the nonclinical data to support a safe starting dose in humans.
- **Animal models with limited utility.** Some classes of therapeutic biologics may have very limited interspecies cross-reactivity or pronounced immunogenicity, or may work by mechanisms that are not known to be conserved between (nonhuman) animals and humans; in these cases, safety data from any animal studies may be very limited in scope and interpretability.

B. Decreasing the Safety Factor

Safety factors of less than 10 may be appropriate under some conditions. The toxicologic testing in these cases should be of the highest caliber in both conduct and design. Most of the time, candidate therapeutics for this approach would be members of a well-characterized class. Within the class, the therapeutics should be administered by the same route, schedule, and duration of administration; should have a similar metabolic profile and bioavailability; and should have similar toxicity profiles across all the species tested including humans. A smaller safety factor might also be used when toxicities produced by the therapeutic are easily monitored, reversible, predictable, and exhibit a moderate-to-shallow dose-response relationship with toxicities that are

Contains Nonbinding Recommendations

consistent across the tested species (both qualitatively and with respect to appropriately scaled dose and exposure).

A safety factor smaller than 10 could be justified when the NOAEL was determined based on toxicity studies of longer duration compared to the proposed clinical schedule in healthy volunteers. In this case, a greater margin of safety should be built into the NOAEL, as it was associated with a longer duration of exposure than that proposed in the clinical setting. This assumes that toxicities are cumulative, are not associated with acute peaks in therapeutic concentration (e.g., hypotension), and did not occur early in the repeat dose study.

VIII. STEP 5: CONSIDERATION OF THE PHARMACOLOGICALLY ACTIVE DOSE

Selection of a PAD depends upon many factors and differs markedly among pharmacological drug classes and clinical indications; therefore, selection of a PAD is beyond the scope of this guidance. However, once the MRSD has been determined, it may be of value to compare it to the PAD derived from appropriate pharmacodynamic models. If the PAD is from an *in vivo* study, an HED can be derived from a PAD estimate by using a BSA-CF. This HED value should be compared directly to the MRSD. If this *pharmacologic* HED is lower than the MRSD, it may be appropriate to decrease the clinical starting dose for pragmatic or scientific reasons. Additionally, for certain classes of drugs or biologics (e.g., vasodilators, anticoagulants, monoclonal antibodies, or growth factors), toxicity may arise from *exaggerated pharmacologic* effects. The PAD in these cases may be a more sensitive indicator of potential toxicity than the NOAEL and might therefore warrant lowering the MRSD.

IX. SUMMARY

A strategy has been proposed to determine the maximum recommended starting dose for clinical trials of new therapeutics in adult healthy volunteers. In summary, usually NOAELs from the relevant animal studies should be converted to the HEDs using the standard factors presented in Table 1. Using sound scientific judgment, a safety factor should be applied to the HED from the most appropriate species to arrive at the MRSD. This process is meant to define the upper limit of recommended starting doses and, in general, lower starting doses can be appropriate. The process described in this guidance should foster consistency among sponsors and Agency reviewers.

Contains Nonbinding Recommendations

REFERENCES

- Boxenbaum, H and C DiLea, 1995, First-Time-in-Human Dose Selection: Allometric Thoughts and Perspectives, *Journal of Clinical Pharmacology*, 35:957-966.
- Burtles, SS, DR Newell, REC Henrar, and TA Connors, 1995, Revisions of General Guidelines for the Preclinical Toxicology of New Cytotoxic Anticancer Agents in Europe, *European Journal of Cancer*, 31A:408-410.
- Contrera, JF, AC Jacobs, RP Hullahalli, M Mehta, WJ Schmidt, and JA DeGeorge, 1995, Systemic Exposure — Based Alternative to the Maximum Tolerated Dose for Carcinogenicity Studies of Human Therapeutics, *Journal of American College of Toxicology*, 14:1-10.
- EPA, 1992, A Cross-Species Scaling Factor for Carcinogen Risk Assessment Based on Equivalence of $\text{Mg/Kg}^{0.75}/\text{Day}$, *Federal Register*, 57:24152-24173.
- Freireich, EJ, EA Gehan, DP Rall, LH Schmidt, and HE Skipper, 1966, Quantitative Comparison of Toxicity of Anticancer Agents in Mouse, Rat, Hamster, Dog, Monkey, and Man, *Cancer Chemotherapy Reports*, 50:219-244.
- Geary, RS, JM Leeds, SP Henry, DK Monteith, and AA Levin, 1997, Antisense Oligonucleotide Inhibitors for the Treatment of Cancer: 1. QUESTION Pharmacokinetic Properties of Phosphorothioate Oligodeoxynucleotides, *Anti-Cancer Drug Design*, 12:383-393.
- Lowe, MC and RD Davis, 1998, The Current Toxicology Protocol of the National Cancer Institute, in K Hellman and SK Carter (eds.), *Fundamentals of Cancer Chemotherapy*, pp. 228-235, New York: McGraw Hill.
- Mahmood, I, MD Green, and JE Fisher, 2003, Selection of the First-Time Dose in Humans: Comparison of Different Approaches Based on Interspecies Scaling of Clearance, 43(7):692-697.
- Mordenti, J, 1986, Man Vs. Beast: Pharmacokinetic Scaling in Mammals, *Journal of Pharmaceutical Sciences*, 75:1028-1040.
- Reigner, BG and KS Blesch, 2002, Estimating the Starting Dose for Entry into Humans: Principles and Practice, *European Journal of Clinical Pharmacology*, 57:835-845.
- Schein, PS, RD Davis, S Carter, J Newman, DR Schein, and DP Rall, 1970, The Evaluation of Anticancer Drugs in Dogs and Monkeys for the Prediction of Qualitative Toxicities in Man, *Clinical Pharmacology and Therapeutics*, 11:3-40.
- Spector, WS (ed.), 1956, *Handbook of Biological Data*, pp. 175, Philadelphia: W.B. Saunders Co.

Contains Nonbinding Recommendations

Stahl, WR, 1967, Scaling of Respiratory Variables in Mammals, *Journal of Applied Physiology*, 22:453-460.

Travis, CC and RK White, 1988, Interspecies Scaling of Toxicity Data, *Risk Analysis*, 8:119-125.

Watanabe, K, FY Bois, and L Zeise, 1992, Interspecies Extrapolation: A Reexamination of Acute Toxicity Data, *Risk Analysis*, 12:301-310.

International Conference on Harmonisation Guidances

ICH guidance for industry *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*

ICH guidance for industry *S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*

ICH guidance for industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*

Contains Nonbinding Recommendations

GLOSSARY

b: Allometric exponent

Body surface area conversion factor (BSA-CF): A factor that converts a dose (mg/kg) in an animal species to the equivalent dose in humans (also known as the *human equivalent dose*), based on differences in body surface area. A BSA-CF is the ratio of the body surface areas in the tested species to that of an average human.

Human equivalent dose (HED): A dose in humans anticipated to provide the same degree of effect as that observed in animals at a given dose. In this guidance, as in many communications from sponsors, the term HED is usually used to refer to the human equivalent dose of the NOAEL. When reference is made to the human equivalent of a dose other than the NOAEL (e.g., the PAD), sponsors should explicitly and prominently note this usage.

K: A dimensionless factor that adjusts for differences in the surface area to weight ratio of species because of their different body shapes.

k_m: Factor for converting mg/kg dose to mg/m² dose

Lowest observed adverse effect level (LOAEL): The lowest dose tested in an animal species with adverse effects.

Maximum recommended starting dose (MRSD): The highest dose recommended as the initial dose in a clinical trial. In clinical trials of adult healthy volunteers, the MRSD is predicted to cause no adverse reactions. The units of the dose (e.g., mg/kg or mg/m²) may vary depending on practices employed in the area being investigated.

Maximum tolerated dose (MTD): In a toxicity study, the highest dose that does not produce unacceptable toxicity.

No observed adverse effect level (NOAEL): The highest dose tested in an animal species that does not produce a significant increase in adverse effects in comparison to the control group. Adverse effects that are biologically significant, even if not statistically significant, should be considered in determining an NOAEL.

No observed effect level (NOEL): The highest dose tested in an animal species with no detected effects.

Pharmacologically active dose (PAD): The lowest dose tested in an animal species with the intended pharmacologic activity.

Safety factor (SF): A number by which the HED is divided to introduce a margin of safety between the HED and the *maximum recommended starting dose*.

W: Body weight in kg

Contains Nonbinding Recommendations

**APPENDIX A:
Analysis of Allometric Exponent on HED Calculations**

An analysis was conducted to determine the effect of the allometric exponent on the conversion of an animal dose to the HED. One can derive the following equation (see Appendix C) for converting animal doses to the HED based on body weights and the allometric exponent (b):

$$\text{HED} = \text{animal NOAEL} \times (W_{\text{animal}}/W_{\text{human}})^{(1-b)}$$

Conventionally, for a mg/m^2 normalization b would be 0.67, but a number of studies (including the original Freireich data) have shown that MTDs scale best across species when $b = 0.75$. The Interagency Pharmacokinetics Group has recommended that $W^{0.75}$ be used for interspecies extrapolation of doses in carcinogenicity studies (EPA 1992). There are no data, however, to indicate the optimal method for converting NOAELs to HEDs. Conversion factors were calculated over a range of animal and human weights using $(W_{\text{animal}}/W_{\text{human}})^{0.33}$ or $(W_{\text{animal}}/W_{\text{human}})^{0.25}$ to assess the effect on starting dose selection of using $b = 0.75$ instead of $b = 0.67$. The results are shown in Table 2. Using an allometric exponent of 0.75 had a big effect on the conversion factor for the smaller species mice and rats. Nonetheless, mice are not commonly used for toxicology studies to support the first-in-human clinical trials. In addition, there is evidence that the area under the plasma concentration versus time curves in rats and humans correlates reasonably well when doses are normalized to mg/m^2 (Contrera et al. 1995). We conclude that the approach of converting NOAEL doses to an HED based on body surface area correction factors (i.e., $b = 0.67$) should be maintained for selecting starting doses for initial studies in healthy volunteers since: (1) mg/m^2 normalization is widely used throughout the toxicology and pharmacokinetic research communities; (2) mg/m^2 normalization provides a more conservative conversion; (3) there are no data to suggest a superior method for converting NOAELs; and (4) CDER has significant experience in establishing safe starting doses based on mg/m^2 , and it is readily calculated.

Species	Weight Range ^b (kg)	Conversion Factors ^c			Ratio of 0.75 to 0.67
		Standard	b = 0.67	b = 0.75	
Mouse	0.018-0.033	0.081	0.075	0.141	1.88
Rat	0.09-0.40	0.162	0.156	0.245	1.57
Rabbit	1.5-3	0.324	0.33	0.43	1.30
Monkey	1.5-4	0.324	0.37	0.47	1.27
Dog	6.5-13.0	0.541	0.53	0.62	1.17

^a conversion factor = $(W_{\text{animal}}/W_{\text{human}})^{(1-b)}$

^b human weight range used was 50-80 kg (110-176 lb)

^c mean conversion factor calculated across entire animal weight range and human weight range

Contains Nonbinding Recommendations

The following summarizes the analysis of the effects of the allometric exponent on HED calculations:

- Changing the allometric exponent from 0.67 to 0.75 had a big effect on the conversion factor for the smaller rodent species; for mice the conversion factors differed by a factor of almost 2.
- Converting doses based on an exponent of 0.75 would lead to higher, more aggressive and potentially more toxic starting doses.
- The limited data available suggest that the most accurate allometric exponent for normalizing MTDs of antineoplastic agents for interspecies extrapolation is $b = 0.75$, but there are no data to indicate the optimal normalization method for interspecies extrapolation of NOAELs in a broad range of therapeutic classes. Using mg/m^2 is widely adopted throughout the drug development community.
- Unless evidence is provided to the contrary, HED calculations should be based on $b = 0.67$ (i.e., the standard conversions based on mg/m^2 relationships).
- There was no notable effect of body weight on calculation of the HED within the weight ranges examined.

Contains Nonbinding Recommendations

APPENDIX B: Analysis of Body Weight Effects on HED Calculations

Accurate conversion of a mg/kg dose to a mg/m² dose depends on the actual weight (and surface area) of the test species. A popular formula for converting doses is:

- (i) $\text{mg/m}^2 = k_m \times \text{mg/kg}$
where $k_m = 100/K \times W^{0.33}$ where K is a value unique to each species (Freireich et al. 1966)
or $k_m = 9.09 \times W^{0.35}$ where a K value unique to each species is not needed (Boxenbaum and DiLea 1995; Burtles et al. 1995; Stahl 1956).

The k_m value is not truly constant for any species, but increases within a species as body weight increases. The increase is not linear, but increases approximately proportional to $W^{2/3}$. For example, the k_m value in rats varies from 5.2 for a 100 g rat to 7.0 for a 250 g rat. Strictly speaking, 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 is preferred. An analysis was undertaken to determine the effect of different body weights within a species on the conversion of an animal dose to the HED using k_m factors. The k_m factor was calculated for a range of body weights using $k_m = 100/K \times W^{0.33}$. In Table 3, a working weight range is shown next to the reference body weight. This is the range within which the HED calculated by using the standard k_m value will not vary more than ± 20 percent from that which would be calculated using a k_m value based on exact animal weight. This is a relatively small variance considering dose separation generally used in deriving the NOAEL, in toxicology studies, which are often twofold separations. For example, suppose a NOAEL in rats is 75 mg/kg and the average rat weight is 250 g. The k_m value for a 250 g rat is 7.0.

$$\text{HED} = 75 \times (7/37) = 14 \text{ mg/kg in humans.}$$

Using the standard k_m value of 6 for rats,

$$\text{HED} = 75 \times (6/37) = 12 \text{ mg/kg in humans.}$$

The HED calculated with the standard k_m value of 6 is within 15 percent of the value calculated using the actual k_m value of 7. As shown in Table 3, the body weights producing k_m factors for which the nominal, integer conversion factor was within 20 percent of the calculated factor covered a broad range. This working weight range encompassed the animal weights expected for the majority of studies used to support starting doses in humans.

Contains Nonbinding Recommendations

Table 3: Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area

Species	Reference Body Weight (kg)	Working Weight Range ^a (kg)	Body Surface Area (m ²)	To Convert Dose in mg/kg to Dose in mg/m ² Multiply by k _m	To Convert Animal Dose in mg/kg to HED ^b in mg/kg, Either	
					Divide Animal Dose By	Multiply Animal Dose By
Human	60	---	1.62	37	---	---
Child ^c	20	---	0.80	25	---	---
Mouse	0.020	0.011-0.034	0.007	3	12.3	0.081
Hamster	0.080	0.047-0.157	0.016	5	7.4	0.135
Rat	0.150	0.080-0.270	0.025	6	6.2	0.162
Ferret	0.300	0.160-0.540	0.043	7	5.3	0.189
Guinea pig	0.400	0.208-0.700	0.05	8	4.6	0.216
Rabbit	1.8	0.9-3.0	0.15	12	3.1	0.324
Dog	10	5-17	0.50	20	1.8	0.541
Primates:						
Monkeys ^d	3	1.4-4.9	0.25	12	3.1	0.324
Marmoset	0.350	0.140-0.720	0.06	6	6.2	0.162
Squirrel monkey	0.600	0.290-0.970	0.09	7	5.3	0.189
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

^a For animal weights within the specified ranges, the HED for a 60 kg human calculated using the standard k_m value will not vary more than ±20 percent from the HED calculated using a k_m value based on the exact animal weight.

^b Assumes 60 kg human. For species not listed or for weights outside the standard ranges, human equivalent dose can be calculated from the formula: HED = animal dose in mg/kg x (animal weight in kg/human weight in kg)^{0.33}.

^c The k_m value is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.

^d For example, cynomolgus, rhesus, and stump-tail.

Contains Nonbinding Recommendations

For the typical species used in nonclinical safety studies, Table 3 also shows the body surface area in m^2 for an animal at a particular *reference weight*. For example, a 400 g guinea pig has a body surface area of approximately $0.05 m^2$. These values come from published sources with surface area determined experimentally by various methods. Compilations of this type of data can be found in published references (Spector 1956).

For animal weights outside the working weight range in Table 3, or for species not included in the table, an alternative method is available for calculating the HED. In these cases the following formula can be used:

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

For example, assume that a NOAEL of 25 mg/kg was determined in a study using rabbits weighing 4.0 kg. The 4.0 kg animals are outside the working range for rabbits of 0.9 to 3.0 kg indicated in Table 3.

$$\text{HED} = 25 \text{ mg/kg} \times (4.0 \div 60)^{0.33} = 25 \times (0.41) = 10 \text{ mg/kg}$$

Alternatively, if the standard conversion factor was used to calculate the HED

$$\text{HED} = 25 \text{ mg/kg} \div 3.1 = 8.1 \text{ mg/kg}$$

The value of 10 mg/kg for the HED is 25 percent greater than the value of 8.1 mg/kg that would be calculated using the standard conversion factor. For example, assume that a NOAEL of 25 mg/kg was determined in a study using rabbits weighing 4.0 kg. The 4.0 kg animals are outside the working range for rabbits of 0.9 to 3.0 kg indicated in Table 3.

$$\text{HED} = 25 \text{ mg/kg} \times (4.0 \div 60)^{0.33} = 25 \times (0.41) = 10 \text{ mg/kg}$$

Alternatively, if the standard conversion factor was used to calculate the HED

$$\text{HED} = 25 \text{ mg/kg} \div 3.1 = 8.1 \text{ mg/kg}$$

The value of 10 mg/kg for the HED is 25 percent greater than the value of 8.1 mg/kg that would be calculated using the standard conversion factor.

The k_m analysis addresses only half of the HED conversion process. The range of human sizes should also be considered to convert the mg/m^2 dose back to an HED dose in mg/kg. To examine the effect of both animal and human weights on the conversion factor, the principle of allometry was used. Interspecies biologic parameters are often related by the power function $Y = aW^b$ where W is body weight and b (allometric exponent) is the slope of the log-log plot, $\log y = b \times \log W + C$. Using algebraic manipulation (see Appendix C), one can derive an equation for converting an animal dose to the HED based on the body weights of the human and the animals for a given allometric exponent. For converting an animal NOAEL in mg/kg to the HED in mg/kg, the equation is:

Contains Nonbinding Recommendations

(ii) $HED = \text{animal NOAEL} \times (W_{\text{animal}}/W_{\text{human}})^{(1-b)}$

Since body surface area is believed to scale with an allometric exponent (b) of 0.67, one can explore how the animal and human body weights affect the conversion factor $(W_{\text{animal}}/W_{\text{human}})^{0.33}$.

The conversion factor was calculated over a range of animal weights and a range of human weights from 50-80 kg. The results are summarized in Table 4. Column B is the weight range of the animals used to calculate, in conjunction with the 50-80 kg range in humans, the conversion factor. The extremes of the conversion factors for the permutations chosen are shown in columns C and D. The proposed standard conversion factors are shown in column E. The percentage difference of these extremes from the standard is shown in column F. Finally, the range of animal weights that produced a conversion factor for a 60 kg human within 20 percent of the standard factor is shown in column G. The ± 10 percent and ± 20 percent intervals across the entire range of weights are graphically illustrated for rats in Table 5.

Table 4: Effect of Body Weight on Human Equivalent Dose Conversions^a						
A	B	C	D	E	F	G
Species	Animal Weight Range ^b (kg)	Conversion Factor ^c			% Difference of Extreme ^e from Standard	$\pm 20\%$ Range ^f for 60 kg Human (kg)
		sm animal lg human	lg animal sm human	Standard ^d		
Mouse	0.018-0.033	0.060	0.089	0.081	-22%	0.015-0.051
Rat	0.090-0.400	0.106	0.213	0.162	-35%	0.123-0.420
Rabbit	1.5-3.0	0.269	0.395	0.324	+22%	1.0-3.4
Monkey	1.5-4.0	0.319	0.435	0.324	+34%	1.0-3.4
Dog	6.5-13.0	0.437	0.641	0.541	-19%	4.7-16.2

^a conversion factor = $(W_{\text{animal}}/W_{\text{human}})^{0.33}$

^b human weight range used was 50-80 kg (110-176 lb)

^c HED in mg/kg equals animal dose in mg/kg multiplied by this value

^d See Table 1

^e extreme from column C or D

^f range of animal weights that produced a calculated conversion factor within 20 percent of the standard factor (column E) when human weight was set at 60 kg

Contains Nonbinding Recommendations

Table 5: Human and Rat Body Weights Producing Body Surface Area Dose Conversion Factors Within 10 Percent and 20 Percent of the Standard Factor (0.162)

EFFECT OF BODY WEIGHT ON BSA-CF							
HED = animal NOAEL · (W _{animal} /W _{human}) ^b exp(1-b), b = 0.67 for mg/m ² conversion							
Standard conversion to mg/kg = 0.162				± 10%	0.146-0.178		
				± 20%	0.130-0.194		
Rat Body Weight (kg)	Human Body Weight (kg)						
	50	55	60	65	70	75	80
0.090	0.124	0.120	0.117	0.114	0.111	0.109	0.106
0.100	0.129	0.125	0.121	0.118	0.115	0.113	0.110
0.110	0.133	0.129	0.125	0.122	0.119	0.116	0.114
0.120	0.137	0.132	0.129	0.125	0.122	0.119	0.117
0.130	0.140	0.136	0.132	0.129	0.126	0.123	0.120
0.140	0.144	0.139	0.135	0.132	0.129	0.126	0.123
0.150	0.147	0.142	0.138	0.135	0.132	0.129	0.126
0.160	0.150	0.146	0.141	0.138	0.134	0.131	0.129
0.170	0.153	0.149	0.144	0.141	0.137	0.134	0.131
0.180	0.156	0.151	0.147	0.143	0.140	0.137	0.134
0.190	0.159	0.154	0.150	0.146	0.142	0.139	0.136
0.200	0.162	0.157	0.152	0.148	0.145	0.141	0.138
0.210	0.164	0.159	0.155	0.151	0.147	0.144	0.141
0.220	0.167	0.162	0.157	0.153	0.149	0.146	0.143
0.230	0.169	0.164	0.159	0.155	0.152	0.148	0.145
0.240	0.172	0.166	0.162	0.157	0.154	0.150	0.147
0.250	0.174	0.169	0.164	0.160	0.156	0.152	0.149
0.260	0.176	0.171	0.166	0.162	0.158	0.154	0.151
0.270	0.179	0.173	0.168	0.164	0.160	0.156	0.153
0.280	0.181	0.175	0.170	0.166	0.162	0.158	0.155
0.290	0.183	0.177	0.172	0.168	0.164	0.160	0.157
0.300	0.185	0.179	0.174	0.179	0.165	0.162	0.158
0.310	0.187	0.181	0.176	0.171	0.167	0.163	0.160
0.320	0.189	0.183	0.178	0.173	0.169	0.165	0.162
0.330	0.191	0.185	0.180	0.175	0.171	0.167	0.163
0.340	0.193	0.187	0.181	0.177	0.172	0.169	0.165
0.350	0.194	0.188	0.183	0.178	0.174	0.170	0.167
0.360	0.196	0.190	0.185	0.180	0.176	0.172	0.168
0.370	0.198	0.192	0.187	0.182	0.177	0.173	0.170
0.380	0.200	0.194	0.188	0.183	0.179	0.175	0.171
0.390	0.202	0.195	0.190	0.185	0.180	0.176	0.173
0.400	0.203	0.197	0.191	0.186	0.182	0.178	0.174
0.410	0.205	0.199	0.193	0.188	0.183	0.179	0.175
0.420	0.207	0.200	0.194	0.189	0.185	0.181	0.177
0.430	0.208	0.202	0.196	0.191	0.186	0.182	0.178
0.440	0.210	0.203	0.197	0.192	0.188	0.183	0.180
0.450	0.211	0.205	0.199	0.194	0.189	0.185	0.181
0.460	0.213	0.206	0.200	0.195	0.190	0.186	0.182

Contains Nonbinding Recommendations

The following are conclusions from these analyses:

- The ± 20 percent interval around the standard conversion factor includes a broad range of animal and human weights.
- Given that the human weights will vary broadly, it is not usually necessary to be concerned about the affect of the variation of animal weights within a species on the HED calculation.
- If an extreme animal weight is encountered in a toxicology study, one can calculate an accurate conversion factor using $(W_{\text{animal}}/W_{\text{human}})^{0.33}$.