Guidance for Industry

Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

July 2005
Pharmacology and Toxicology

Regeneron Ex. 2109
Alvotech v. Regeneron
PGR2025-00085

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Contains Nonbinding Recommendations

Guidance for Industry[1]
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I. INTRODUCTION

This guidance outlines a process (algorithm) and vocabulary for deriving the maximum recommended starting dose (MRSD) for *first-in-human* clinical trials of new molecular entities in adult healthy volunteers, and recommends a standardized process by which the MRSD can be selected. The purpose of this process is to ensure the safety of the human volunteers.

The goals of this guidance are to: (1) establish a consistent terminology for discussing the starting dose; (2) provide common conversion factors for deriving a human equivalent dose (HED); and (3) delineate a strategy for selecting the MRSD for adult healthy volunteers, regardless of the projected clinical use. This process is depicted in a flow chart that presents the decisions and calculations used to generate the MRSD from animal data (see Appendix E).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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II. BACKGROUND

The process identified in this guidance pertains to determining the MRSD for adult healthy subjects when beginning a clinical investigation of any new drug or biological therapeutic that has been studied in animals. This guidance is not pertinent to endogenous hormones and proteins (e.g., recombinant clotting factors) used at physiologic concentrations or prophylactic vaccines. The process outlined in this guidance pertains primarily to drug products for which systemic exposure is intended; it does not address dose escalation or maximum allowable doses in clinical trials.

Although the process outlined in this guidance uses administered doses, observed toxicities, and an algorithmic approach to calculate the MRSD, an alternative approach could be proposed that places primary emphasis on animal pharmacokinetics and modeling rather than dose (Mahmood et al. 2003; Reigner and Blesch 2002). In a limited number of cases, animal pharmacokinetic data can be useful in determining initial clinical doses.[2] However, in the majority of investigational new drug applications (INDs), animal data are not available in sufficient detail to construct a scientifically valid, pharmacokinetic model whose aim is to accurately project an MRSD.

Toxicity should be avoided at the initial clinical dose. However, doses should be chosen that allow reasonably rapid attainment of the phase 1 trial objectives (e.g., assessment of the therapeutic's tolerability, pharmacodynamic or pharmacokinetic profile). All of the relevant preclinical data, including information on the pharmacologically active dose, the full toxicologic profile of the compound, and the pharmacokinetics (absorption, distribution, metabolism, and excretion) of the therapeutic, should be considered when determining the MRSD. Starting with doses lower than the MRSD is always an option and can be particularly appropriate to meet some clinical trial objectives.

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[2] If the parent drug is measured in the plasma at multiple times and is within the range of toxic exposures for two or more animal species, it may be possible to develop a pharmacokinetic model predicting human doses and concentrations and to draw inferences about safe human plasma levels in the absence of prior human data. Although quantitative modeling for this purpose may be straightforward, the following points suggest this approach can present a number of difficulties when estimating a safe starting dose. Generally, at the time of IND initiation, there are a number of unknowns regarding animal toxicity and comparability of human and animal pharmacokinetics and metabolism: (1) human bioavailability and metabolism may differ significantly from that of animals; (2) mechanisms of toxicity may not be known (e.g., toxic accumulation in a peripheral compartment); and/or (3) toxicity may be due to an unidentified metabolite, not the parent drug. Therefore, relying on pharmacokinetic models (based on the parent drug in plasma) to gauge starting doses would require multiple untested assumptions. Modeling can be used with greatest validity to estimate human starting doses in special cases where few underlying assumptions would be necessary. Such cases are exemplified by large molecular weight proteins (e.g., humanized monoclonal antibodies) that are intravenously administered, are removed from circulation by endocytosis rather than metabolism, have immediate and detectable effects on blood cells, and have a volume of distribution limited to the plasma volume. In these cases, allometric, pharmacokinetic, and pharmacodynamic models have been useful in identifying the human mg/kg dose that would be predicted to correlate with safe drug plasma levels in nonhuman primates. Even in these cases, uncertainties (such as differences between human and animal receptor sensitivity or density) have been shown to affect human pharmacologic or toxicologic outcomes, and the use of safety factors as described in this guidance is still warranted.

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The remainder of this guidance focuses on the recommended algorithmic process for starting dose extrapolation from animals to humans based on administered doses, since this method will likely be useful for the majority of INDs seeking to investigate new drugs in healthy volunteers. Some classes of drugs (e.g., many cytotoxic or biological agents) are commonly introduced into initial clinical trials in patient volunteers rather than healthy volunteers. Typically, patients are used instead of healthy volunteers when a drug is suspected or known to be unavoidably toxic. This guidance does not address starting doses in patients. However, many principles and some approaches recommended here may be applicable to designing such trials.

III. OVERVIEW OF THE ALGORITHM

The recommended process for selecting the MRSD is presented in Appendix E and described in this section. The major elements (i.e., the determination of the no observed adverse effect levels (NOAELs) in the tested animal species, conversion of NOAELs to HED, selection of the most appropriate animal species, and application of a safety factor) are all discussed in greater detail in subsequent sections. Situations are also discussed in which the algorithm should be modified. The algorithm is intended to be used for systemically administered therapeutics. Topical, intranasal, intratissue, and compartmental administration routes and depot formulations can have additional considerations, but similar principles should apply.

The process of calculating the MRSD should begin after the toxicity data have been analyzed. Although only the NOAEL should be used directly in the algorithm for calculating an MRSD, other data (exposure/toxicity relationships, pharmacologic data, or prior clinical experience with related drugs) can affect the choice of most appropriate species, scaling, and safety factors.

The NOAEL for each species tested should be identified, and then converted to the HED using appropriate scaling factors. For most systemically administered therapeutics, this conversion should be based on the normalization of doses to body surface area. Although body surface area conversion is the standard way to approximate equivalent exposure if no further information is available, in some cases extrapolating doses based on other parameters may be more appropriate. This decision should be based on the data available for the individual case. The body surface area normalization and the extrapolation of the animal dose to human dose should be done in one step by dividing the NOAEL in each of the animal species studied by the appropriate body surface area conversion factor (BSA-CF). This conversion factor is a unitless number that converts mg/kg dose for each animal species to the mg/kg dose in humans, which is equivalent to the animal's NOAEL on a mg/m^2 basis. The resulting figure is called a human equivalent dose (HED). The species that generates the lowest HED is called the most sensitive species.

When information indicates that a particular species is more relevant for assessing human risk (and deemed the *most appropriate species*), the HED for that species may be used in subsequent calculations, regardless of whether this species is the most sensitive. This situation is more applicable to biologic therapies, many of which have high selectivity for binding to human target

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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 details[3]). (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/m^2 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.

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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

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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/m^2) (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 (LD_{10}s) and MTDs in nonrodents both correlated with the human MTD when the doses were normalized to the same administration schedule and expressed as mg/m^2. 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/m^2 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

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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.)

Table 1: Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area

Species	To Convert Animal Dose in mg/kg to Dose in mg/m², 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:

HED = animal dose in mg/kg x (animal weight in kg/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 stumptail.

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

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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,

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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

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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.

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- **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

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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.

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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/m^2 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/m^2) 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

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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):

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

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 $(W_{animal}/W_{human})^{0.33}$ or $(W_{animal}/W_{human})^{0.25}$ 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.

Table 2: Effect of Allometric Exponent on Conversion Factor[a]

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 = $(W_{animal}/W_{human})^{(1-b)}$

[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

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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.

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APPENDIX B:
Analysis of Body Weight Effects on HED Calculations

Accurate conversion of a mg/kg dose to a mg/m^2 dose depends on the actual weight (and surface area) of the test species. A popular formula for converting doses is:

(i) $mg/m^2 = k_m \times mg/kg$
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 relativity 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.

HED = 75 × (7/37) = 14 mg/kg in humans.

Using the standard k_m value of 6 for rats,

HED = 75 × (6/37) = 12 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.

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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 stumptail.

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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:

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

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 $(W_{animal}/W_{human})^{0.33}$.

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	±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 = $(W_{animal}/W_{human})^{0.33}$

[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

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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})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

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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 $(W_{animal}/W_{human})^{0.33}$.

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APPENDIX C:
Derivation of the Interspecies Scaling Factor $(W_a/W_h)^{(1-b)}$

Power equation $(mg) = aW^b$

$\log(mg) = \log(a) + b \bullet \log(W) = b \bullet \log(W) + c$

Given the weights of animal and human, and animal dose in mg/kg, solve for HED in mg/kg:

Let H = mg/kg dose in humans
A = mg/kg dose in animals
W_h = weight of human
W_a = weight of animal

for animal	$\log(mg) = \log(a) + b \bullet \log(W_a) = b \bullet \log(W_a) + c$
replace mg	$\log(A \bullet W_a) = b \bullet \log(W_a) + c$
solve for c	$c = \log(A \bullet W_a) - b \bullet \log(W_a)$
	$= \log(A) + \log(W_a) - b \bullet \log(W_a)$
	$= \log(A) + (1-b)\log(W_a)$
likewise for human	$c = \log(H) + (1-b)\log(W_h)$
equate two equations	$\log(A) + (1-b)\log(W_a) = \log(H) + (1-b)\log(W_h)$
solve for log(H)	$\log(H) = \log(A) + (1-b)\log(W_a) - (1-b)\log(W_h)$
	$= \log(A) + (1-b)[\log(W_a) - \log(W_h)]$
	$= \log(A) + \log[(W_a/W_h)^{(1-b)}]$
	$\log(H) = \log[A \bullet (W_a/W_h)^{(1-b)}]$
solve for H	$H = A \bullet (W_a/W_h)^{(1-b)}$

For example, using mg/m^2 normalization (b = 0.67) the predicted human MTD in mg/kg based on a rat LD_{10} in mg/kg is $MTD = LD_{10} \bullet (W_a/W_h)^{0.33}$.

Likewise the HED in mg/kg based on a surface area conversion given an animal NOAEL is $HED = NOAEL \bullet (W_a/W_h)^{0.33}$.

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APPENDIX D:
Examples of Calculations for Converting Animal Doses to Human Equivalent Doses

This appendix provides examples of specific calculations to be taken in deriving an HED based on standardized factors.

Tables 1 and 3 provide standardized conversion factors for changing animal or human doses expressed as mg/kg to doses expressed as mg/m^2. Tables 1 and 3 also have factors (and divisors) for converting animal doses in mg/kg to the human dose in mg/kg that is equivalent to the animal dose if both were expressed on a mg/m^2 basis. This human dose in mg/kg is referred to as the HED.

Example 1: Converting to mg/m^2 HED

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). The k_m factor has units of kg/m^2; it is equal to the body weight in kg divided by the surface area in m^2.

formula:	$mg/kg \times k_m = mg/m^2$
to convert a dose of 30 mg/kg in a dog:	$30 \times 20 = 600\ mg/m^2$
to convert a dose of 2.5 mg/kg in a human:	$2.5 \times 37 = 92.5\ mg/m^2$

Example 2: Converting to mg/kg HED in two steps

To calculate the HED for a particular dose in animals, one can calculate the animal dose in mg/m^2 by ***multiplying*** the dose in mg/kg by the k_m factor for that species as described in Example 1. The dose can then be converted back to mg/kg in humans by ***dividing*** the dose in mg/m^2 by the k_m factor for humans.

formula: (animal mg/kg dose × animal k_m) ÷ human k_m = human mg/kg dose
to calculate the HED for a 15 mg/kg dose in dogs:
$(15 \times 20) \div 37 = 300\ mg/m^2 \div 37 = 8$ mg/kg

Example 3: Converting to mg/kg HED in one step

The calculation in Example 2 can be simplified by combining the two steps. The HED can be calculated directly from the animal dose by ***dividing*** the animal dose by the ratio of the human/animal k_m factor (third column in Table 1) or by ***multiplying*** by the ratio of the animal/human k_m factor (fourth column in Table 1).

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Division method

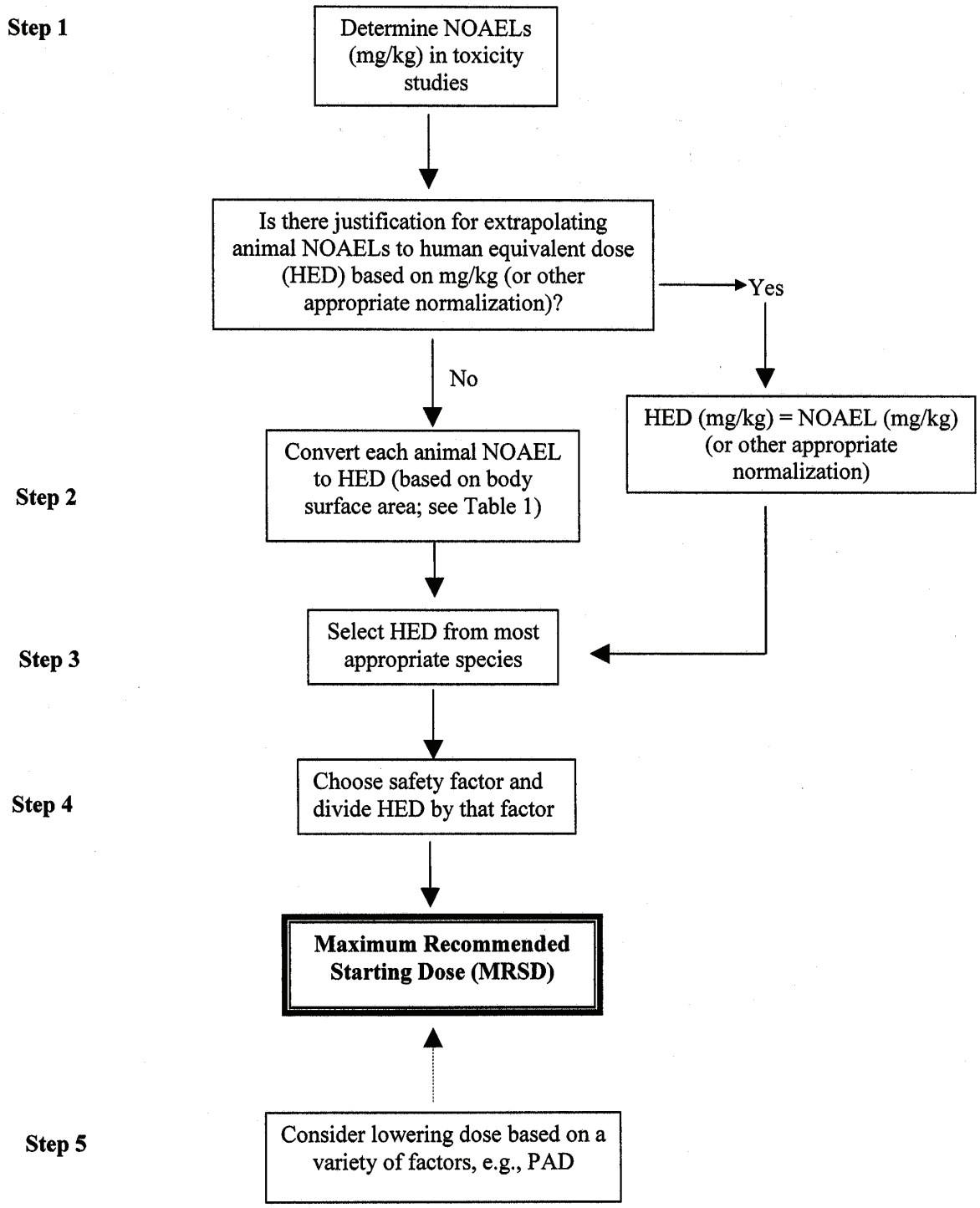
NOAEL	calculation	HED
	mg/kg ÷ [$k_{mhuman}/k_{manimal}$]	
15 mg/kg in dogs	15 mg/kg ÷ 1.8 =	8 mg/kg
50 mg/kg in rats	50 mg/kg ÷ 6.2 =	8 mg/kg
50 mg/kg in monkeys	50 mg/kg ÷ 3.1 =	16 mg/kg

Multiplication method

NOAEL	calculation	HED
	mg/kg × [$k_{manimal}/k_{mhuman}$]	
15 mg/kg in dogs	15 mg/kg × 0.541 =	8 mg/kg
50 mg/kg in rats	50 mg/kg × 0.162 =	8 mg/kg
50 mg/kg in monkeys	50 mg/kg × 0.324 =	16 mg/kg

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APPENDIX E:
Selection of Maximum Recommended Starting Dose for Drugs Administered Systemically to Normal Volunteers



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