Guidance for Industry and Reviewers

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

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

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, and (3) delineate a strategy for selecting the MRSD for adult healthy volunteers, regardless of the projected clinical use. This process is diagrammed with a flow chart that presents the decisions and calculations used to generate the MRSD from animal data.

II. SCOPE

The process identified in this document 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 document is not pertinent to prophylactic vaccines or endogenous proteins (i.e., recombinant clotting factors) used at physiologic concentrations. The process outlined in this document does not address dose escalation or maximum allowable doses in clinical trials.

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

Although the process outlined in this document uses observed toxicities, administered doses, 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. In a limited number of cases, animal pharmacokinetic data may be useful in determining initial clinical doses.[2] However, in the majority of new 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 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 a possible option and may be particularly appropriate to meet some clinical trial objectives.

The remainder of this document will focus 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 new 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, this occurs when a drug is suspected or known to be unavoidably toxic. Although this document does not specifically address starting doses in patients, many principles and some approaches recommended here may be applicable to designing such trials.

[2] If the parent drug is measured in the plasma at multiple times and fits the range of toxic dose for two or more animal species, it may be possible to develop a pharmacokinetic model predicting human doses and concentrations and draw inferences about human safe plasma levels in the absence of prior human data. While quantitative modeling for this purpose may be straightforward, the following points suggest this approach may present a number of difficulties when evaluating estimates of 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 (i.e., toxic accumulation in a peripheral compartment; and/or (3) toxicity may be due to an unidentified metabolite, not parent drug. Thus, to rely on pharmacokinetic models (based on parent drug in plasma) to gauge starting doses would require multiple untested assumptions. Modeling may 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 (like humanized monoclonal antibodies), which are intravenously administered, are removed from circulation by endocytosis rather than metabolizism, have immediate and detectable effects on blood cells, and have a volume of distribution limited to the plasma volume. Here, 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 chimpanzee receptor sensitivity or density) have been shown to affect human pharmacologic or toxicologic outcomes, and the use of safety factors as described in this document is still warranted.

III. OVERVIEW OF THE ALGORITHM

The process for selecting the MRSD is presented in Figure 1 and described in this section. The major elements C the determination of the no observed adverse effect levels (NOAELs) in the tested species, conversion of NOAELs to human equivalent dose (HED), selection of the most appropriate species, and application of a safety factor C 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, intra-tissue, and compartmental administration routes and depot formulations may 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 a 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, then each should be converted to the human equivalent dose (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 usual 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 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 most relevant for assessing human risk (and deemed the *most appropriate species*), the HED for that species should be used in subsequent calculations, regardless of whether this species was the most sensitive. This case is common for biologic therapies, many of which have high selectivity for binding to human target proteins, and limited reactivity in species commonly used for toxicity testing. In such cases, in vitro binding and activity studies should be done to select appropriate, relevant species before toxicity studies are designed (please refer to the ICH[3] guidance for industry *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* for more details). Additionally, a species might be considered an inappropriate toxicity model for a given drug if a dose-limiting toxicity in that species was concluded to be of limited value for human risk assessment (based on historical comparisons of toxicities in species to those in humans across a therapeutic class). In

[3] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

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 (such as severe headaches) in humans can be significant dose-limiting toxicities that may go undetected in animal studies.

In general, a safety factor of 10 is recommended. 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 of 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 here will derive the maximum recommended starting dose. This algorithm generates a 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 document (Table one, 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.

The remainder of this document provides a description of the individual steps in the recommended process and the reasoning behind each step. The method is supported by a general review and analysis by CDER and CBER examining the results from a number of therapeutics entered into development.

IV. STEP 1: NO OBSERVED ADVERSE EFFECT LEVEL (NOAEL) 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 differing definitions of NOAEL exist, but for selecting a starting dose, the following is used here: the highest dose level that does not produce a significant increase in adverse effects. In this context, adverse effects that are statistically significant and adverse effects that may be clinically 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 adverse ones, 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 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 human data or formal allometric comparison of pharmacokinetics. Measurements of systemic levels or exposure (i.e., AUC or Cmax) 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 data on bioavailability, metabolite profile, and plasma drug levels associated with toxicity may influence the choice of the NOAEL. One such case would be when saturation of drug absorption occurs at a dose that produces no toxicity. In this case, the lowest saturating dose, not the highest (non-toxic) 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 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 (HED) CALCULATION

A. Conversion Based on Body Surface Area

After the NOAELs in the relevant animal studies have been determined, they are converted to human equivalent doses (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 or NOAEL, are usually

assumed to scale well between species when doses are normalized to body surface area (i.e., mg/m^2). The basis for this assumption lies primarily with the work of Freireich et al. (1996) 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 non-rodents 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), normalization to body surface area has remained a widespread practice for estimating an HED based on an animal dose.

An analysis of the impact 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 surface area approach 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 from each species should be standardized. Since surface area varies with $W^{0.67}$, the conversion factors are therefore 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 (body surface area - conversion factor) 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, below, are therefore recommended as the standard values to be used for interspecies dose conversions for NOAELs in CDER and CBER. 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 (HED) Based on Body Surface Area

Species	To convert animal dose in mg/kg to dose in mg/m^2, multiply by km below:	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, human equivalent dose can be calculated from the formula:

HED = animal dose in mg/kg x (animal weight in kg/human weight in kg)$^{0.33}$.

[b] This km is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.

[c] For example, cynomolgus, rhesus, 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 factors below should be satisfied before extrapolating to the HED on a mg/kg basis rather than using the mg/m^2 approach. Note that mg/kg scaling will give a 12-, 6-, and 2- fold higher HED than the default mg/m^2 approach for mice, rats, and dogs, respectively. If these factors cannot be met, 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).

2. If only two NOAELs from toxicology studies in separate species are available, one of the following criteria should also be true:

   - The therapeutic is administered orally and the dose is limited by local toxicities. Gastrointestinal (GI) compartment weight scales by $W^{0.94}$. GI

volume determines the concentration of the therapeutic in the GI tract. It is thus 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 Cmax (Geary et al., 1997). For some antisense drugs, the Cmax 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.

C. Other Exceptions to Mg/M^2 Scaling Between Species

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 (mg/area of application, for instance) 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, intraocular, intrapleural, and intraperitoneal administration. Such therapeutics should be normalized between species according to the compartmental volumes and concentrations of the therapeutic.
3. Biological products 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 elimination (ADME) of the therapeutic between the species; (2) class experience that may indicate a particular model is predictive of human toxicity; or (3) limited biological cross-species pharmacologic reactivity of the therapeutic. This latter point is especially important for

biological therapeutics as many are human proteins that bind to human or non-human primate targets (see ICH guidance S6).

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, (i.e., 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. Similarities of biochemistry and physiology between the species and humans that are relevant to the limiting toxicities of the therapeutic should also be considered under class experience. If a species is the most sensitive but has differences in physiology compared to humans that sensitize it to the therapeutic, it may not be the most appropriate species for selecting the MRSD.

VII. STEP 4: APPLICATION OF SAFETY FACTOR

Once the HED of the NOAEL in the most appropriate species has been determined, a safety factor is then applied in order 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 animal toxicity studies to studies in humans resulting from: (1) uncertainties due to enhanced sensitivity to therapeutic 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 absorption, distribution, metabolism, and excretion of the therapeutic. These differences may be accommodated by lowering the human starting dose from the HED of the selected species NOAEL.

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

While a safety factor of 10 can generally be considered adequate for protection of human subjects participating in initial clinical trials, this safety factor 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 due to 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 the 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 prodromal indicators. 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.

Variable bioavailability. Widely divergent bioavailability in the several species, with 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 AUC levels eliciting effect. When doses or exposure levels that produce a toxic effect differ greatly across species, the ability to predict a toxic level in humans is reduced and a greater safety factor may be called for.

Questionable study design or conduct. Poor study design or conduct casts doubt on the accuracy of the conclusions drawn from the data. For instance, few dose levels, wide dosing intervals, or large differences in responses between 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 crossreactivity 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 consistent across the tested species (both qualitatively and with respect to appropriately scaled dose and exposure).

An additional factor that could suggest a safety factor smaller than 10 would be a case where 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 is often 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 (PAD)

Once the MRSD has been determined, it may be of value to compare it to the PAD derived from pharmacodynamic models. If the PAD is from an in vivo study, an HED can be derived from a PAD estimate by using a body surface area conversion factor (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 highest 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 document should foster consistency among sponsors and Agency reviewers.

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International Conference on Harmonisation guidances

S6 *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*

S3A Toxicokinetics: The assessment of System Exposure in Toxicity Studies

M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

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. 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 clinical trials in humans. 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. It is concluded 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) the centers have significant experience in establishing safe starting does 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

To summarize this 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 two.

- Converting doses based on an exponent of 0.75 would lead to higher, more aggressive and potentially more dangerous starting doses.

- The limited data available suggest that the most accurate allometric exponent for normalizing maximally tolerated doses (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 therefore be based on b=0.67, i.e., the standard conversions based on mg/m^2 relationships.

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) $mg/m^2 = km \times mg/kg$

where $km = 100/K \times W^{0.33}$ where K is a value unique to each species

or $km = 9.09 \times W^{0.35}$ where a K value unique to each species is not needed.

The km 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 *km* in rats varies from 5.2 for a 100 g rat to 7.0 for a 250 g rat. Strictly speaking, the km value of 6 applies only to rats at the *reference weight* of 150 g. For standardization and practical purposes, a fixed km 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 km factors. The km factor was calculated for a range of body weights using $km = 100/K \times W^{0.33}$. In Table 3 (see next page), 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 km value will not vary more than ±20 percent from that which would be calculated using a km 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 2-fold separations. For example, suppose a NOAEL in rats is 75 mg/kg and the average rat weight is 250 g. The km for a 250 g rat is 7.0.

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

Using the standard *km* of 6 for rats,

$HED = 75 \times (6/37) = 12$ mg/kg in humans,

The HED calculated with the standard km of 6 is within 15 percent of the value calculated using the actual km of 7. As shown in Table 3, the body weights producing km 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.

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.

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:

596

Table 3: Conversion of Animal Doses to Human Equivalent Doses (HED) 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 *km* below:	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	350	0.140-0.720	0.06	6	6.2	0.162
squirrel monkey	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

597 [a] For animal weights within the specified ranges, the HED for a 60 kg human calculated using the standard km value will not vary more than ±20
598 percent from the HED calculated using a km based on the exact animal weight.
599 [b] Assumes 60 kg human. For species not listed or for weights outside the standard ranges, human equivalent dose can be calculated from the
600 formula: HED = animal dose in mg/kg x (animal weight in kg/human weight in kg)$^{0.33}$.
601 [c] The km is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.
602 [d] For example, cynomolgus, rhesus, stumptail, etc

HED = Animal dose (mg/kg) × [animal weight (kg) ÷ 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.

HED = 25 mg/kg × (4.0 ÷ 60)$^{0.33}$ = 25 × (0.41) = 10 mg/kg

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

HED = 25 mg/kg ÷ 3.1 = 8.1 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 km analysis addresses only half of the HED conversion process. The range of human sizes must also be considered to convert the mg/m^2 dose back to a 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, this equation is:

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

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, next page. 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 are shown in column G. The ±10 percent and ±20 percent intervals across the entire range of weights are graphically illustrated for rats in the attached spreadsheet (see Table 5).

643

Table 4: Effect of Body Weight on HED Conversions[a]

A	B	C	D	E	F	G
species	animal weight range[b] (kg)	conversion factor[c]: sm animal lg human	conversion factor[c]: lg animal sm human	conversion factor[c]: Standard[d]	% difference of extreme[e] from standard	±20% range[f] for 60 kg human (kg)
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

644

645 [a] conversion factor = $(W_{animal}/W_{human})^{0.33}$
646 [b] human weight range used was 50-80 kg (110-176 lb)
647 [c] HED in mg/kg equals animal dose in mg/kg multiplied by this value
648 [d] See Table 1
649 [e] extreme from column C or D
650 [f] range of animal weights that produced a calculated conversion factor within 20% of the standard
651 factor (column E) when human weight was set at 60 kg
652

653 **The conclusions from these analyses are:**

654 • The ±20 percent interval around the standard conversion factor includes a broad range
655 of animal and human weights.
656

657 • Given that the human weights will vary broadly, it is not usually necessary to be
658 concerned about the impact of the variation of animal weights within a species on the
659 HED calculation.
660

661 • If an extreme animal weight is encountered in a toxicology study, one can calculate
662 an accurate conversion factor using $(W_{animal}/W_{human})^{0.33}$.

663 **Table 5: Human and Rat Body Weights Producing Body Surface Area Dose Conversion Factors**
664 **Within 10 percent and 20 percent of the Standard Factor (0.162)**
665

RAT							
Effective of body weights on BSA-CF							
	Use HED = animal NOAEL • $(W_{animal}/W_{human})exp(1-b)$						
	assuming b=		**0.67**	for mg/m2 conversion			
standard conversion to mg/kg =			0.162	±10%	0.146-0.178		
				±20%	0.130-0.194		
Body Weight (kg)							
human (kg)							
rat (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	0.170	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

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:
$HED = NOAEL \bullet (W_a/W_h)^{0.33}$

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 km (for mass constant). The km 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 × *km* = mg/m^2
to convert a dose of 30 mg/kg in a dog:	30 × 20 = 600 mg/m^2
to convert a dose of 2.5 mg/kg in a human:	2.5 × 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 *km* 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 km for humans.

formula:	(Animal mg/kg dose × animal *km*) ÷ human *km* = human mg/kg dose
to calculate the HED for a 15 mg/kg dose in dogs:	(15 × 20) ÷ 37= 300 mg/m^2 ÷ 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 km (third column in Table 1) or by ***multiplying*** by the ratio of animal/human km (fourth column in Table 1).

Division method

NOAEL	calculation	HED
	mg/kg ÷ [km_{human}/km_{animal}]	
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 × [km_{animal}/km_{human}]	
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 monkey	50 mg/kg × 0.324 =	16 mg/kg

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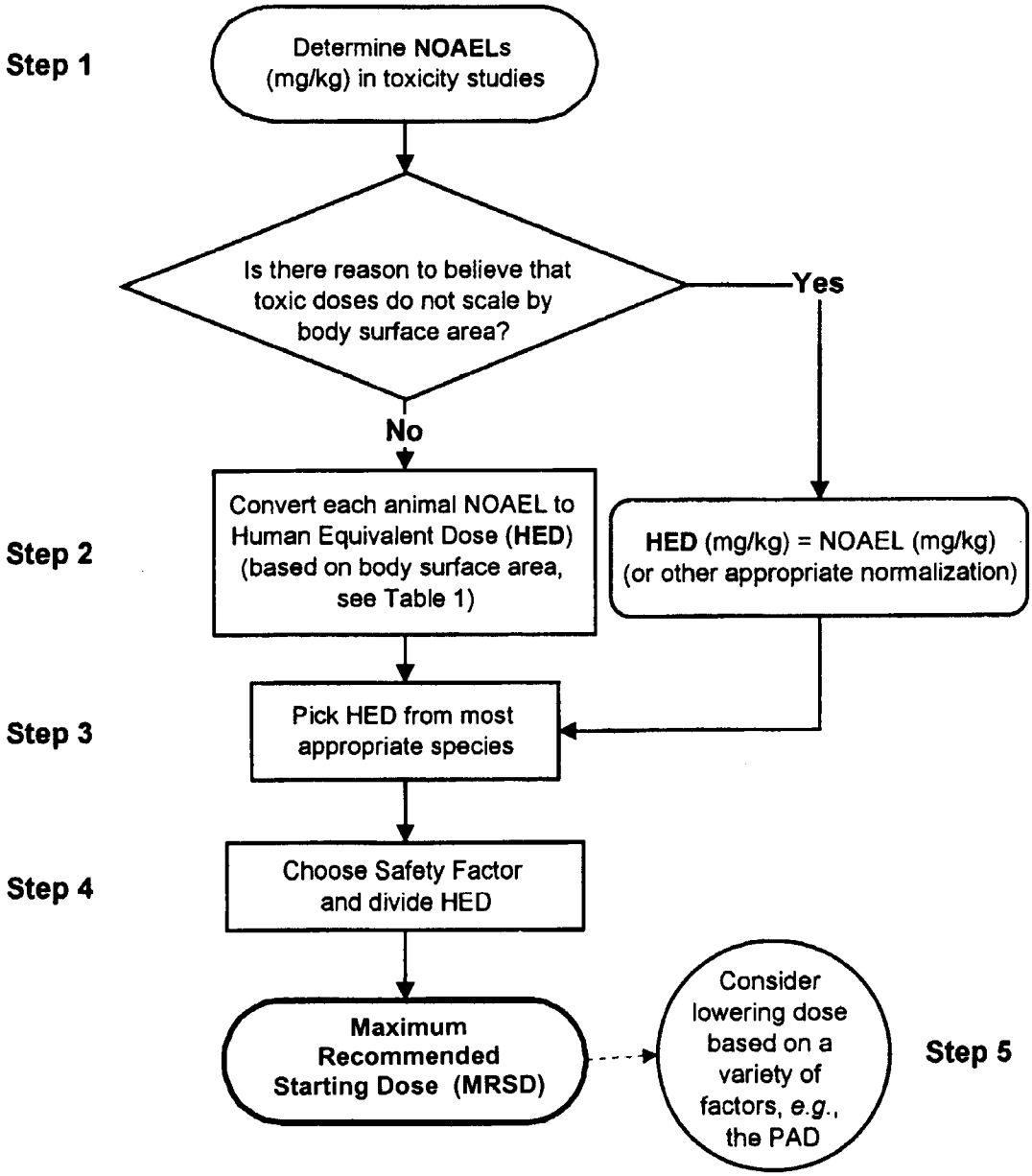
APPENDIX E

Selection of Maximum Recommended Starting Dose

for drugs administered systemically to normal volunteers



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GLOSSARY

B: Allometric exponent

BSA-CF: Body surface area conversion factor: 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

HED: Human equivalent dose: a dose in humans anticipated to provide the same degree of effect as that observed in animals at a given dose. In this document, 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 due to their different body shapes

Km: Factor for converting mg/kg dose to mg/m^2 dose

LOAEL: Lowest observable adverse effect level: the lowest dose tested in an animal species with adverse effects

MRSD: Maximum recommended starting dose: 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**.**

MTD: Maximum tolerated dose in toxicity studies: a dose that is significantly toxic.

NOAEL: No observed adverse effect level: the highest dose tested in an animal species without adverse effects detected

NOEL: No observed effect level: the highest dose tested in an animal species with no detected effects

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

SF: Safety factor: 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