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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 02D-0492; Draft Guidance, *Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers;* 68 Federal Register 2340 (January 16, 2003)

Dear Sir/Madam:

The following comments on the above noted draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2001, our members invested over $30 billion in the discovery and development of new medicines.

PhRMA hopes that our general and specific comments on this draft guidance are helpful to the Agency as it moves forward to finalize the document.

Sincerely,

Alan Goldhammer

02D-0492 C4

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General Comments

PhRMA agrees with the general assumptions of Lines 48-53, that toxicity should be avoided at the initial dose, and that all of the relevant preclinical data should be considered when determining the maximum recommended starting dose (MRSD). PhRMA also endorses the effort to establish a consistent terminology for discussing the starting dose, and the comprehensive discussion of important factors that must be considered in choosing a starting dose for human studies.

However, there are many approaches to choosing a starting dose for first introduction to man studies. These include not only the algorithmic approach outlined in the draft guidance (and many variations of this approach), but also methods using the availability of animal pharmacokinetics, methods to use allometric scaling to predict pharmacokinetics in man, use of pharmacokinetic (PK) or pharmacodynamic (PD) information from related compounds in a class, and other methods as well. These approaches are summarized more completely in a recent review paper[1]. While this guidance is thoughtful and does provide a comprehensive discussion of important safety factors in choosing a first clinical dose, it does so only in the context of this one algorithmic approach.

In particular, alternative approaches that place "primary emphasis on animal pharmacokinetics and modeling rather than dose (lines 41-42)" are also important information to take into account when choosing a starting dose in man. PhRMA was surprised by the comment that "...in a majority of new INDs, animal data is not available in sufficient detail to construct a scientifically valid, pharmacokinetic model whose aim is to accurately project an MRSD (line 44-46)." If such information were available, an algorithm for choosing a starting dose is less relevant, and the guidance should clearly recognize these alternative approaches. This is consistent with a widely published conference report authored in part by FDA staff promoting the use of pharmacokinetics, pharmacodynamics and toxicokinetics in rational drug development.[2] The guidance in its current form could inhibit further progress in this area by its sole reliance on an empiric algorithm.

This guidance makes several key assumptions (e.g., decision to focus primarily on body surface area [mg/m^2] as the primary method of scaling, safety factor of ~10, human dose calculated in mg/kg) for which little, if any supporting information is provided. Conspicuous by its absence are any data outlining starting dose choices in IND submissions and subsequent follow-up (and in particular, any analysis of the usefulness of this *vs.* alternative methods), though the Draft Guidance states (lines 138-139) that "this method is supported by general review and analysis by CDER and CBER." PhRMA respectfully suggests that this review should be referenced (if feasible) or made available for more general review while protecting proprietary information. Even better would be making this a focus of meetings with PhRMA or alternative venues to fully explore the information supporting this approach in an open forum, so the many alternative views on this subject could be openly discussed.

The proposed method of estimation of human equivalent dose (HED), based on a power function of body weight, assumes that all absorption and elimination processes scale across species for all drugs by this one relationship. It may predict HED reasonably for drugs which are cleared by renal filtration, or which demonstrate high hepatic extraction (such that clearance

is a function of hepatic blood flow). However, it is uncertain if it will provide reliable estimates for drugs which undergo active secretion/re-absorption in the kidney or liver, or for many drugs which are metabolized in the liver but demonstrate low hepatic clearance. As such this estimate, which is easily calculated, should be only one of several estimates that are considered prior to estimation of the HED.

Finally, consideration of pharmacologic effects has not been given enough emphasis or prominence in the document. This is important as, in practice, a starting dose is often chosen based on lack of expected pharmacologic effects.

Specific Comments

I. Introduction

Line 19. It may be too simplistic to try to reduce this difficult decision to an 'algorithm'.

Lines 26-27. It is not clear that defining an MRSD "regardless of the projected clinical use" is an appropriate objective. For certain types of indications (cancer, HIV), "reasonably rapid attainment of Phase I trial objectives (line 49)" are much more important than for other indications for which safety is the only imperative. Thus, indication should be an important determinant in decisions about starting dose.

II. Scope

Lines 33-35: Please clarify if the scope is limited to the first introduction to healthy subjects, or the first introduction of a specific drug in US IND studies? Specifically, if preliminary human pharmacokinetic data are generated outside the US, please clarify that the first IND study is not subject in any way to this guidance, since human pharmacokinetic data would be available.

Lines 37-38: Because dose escalation, maximum allowable doses and starting doses are highly related, the document may be more useful if all were addressed.

Lines 40-46 and footnote: The comments on the limited availability and usefulness of animal pharmacokinetic data are puzzling. ICH M3 recommends the evaluation of toxicokinetic data prior to human clinical trials and encourages the comparison of metabolic pathways in animals and humans. In fact, prior to clinical evaluation, most NCEs have been selected from large series of compounds. To reduce later stage attrition rates, pharmaceutical companies now include various PK and metabolic properties (extending to PK/PD modeling), which are becoming increasingly predictive of the clinical situation, in this selection procedure. PhRMA company experience suggests that sufficient pharmacokinetic and toxicokinetic data to estimate drug exposure in the relevant preclinical species are included in INDs. If something else is intended by the term "pharmacokinetic model," this should be explained. The case for limited usefulness of pharmacokinetic data appears to be based on the fact that there are a number of unknowns when predicting human pharmacokinetics and toxicity from animal data. It should be noted that the use of dose suffers from essentially the same uncertainties and that the proposed algorithm is simply another type of model (with possibly more assumptions). These

issues are best addressed by using conservative assumptions and applying a safety factor regardless of whether the underlying calculations use concentration or dose as a measure of exposure. It seems that using data from one species and scaling based on BSA to choose an equivalent dose in humans would provide a less precise estimate than using exposure data from several species. Data (or a reference) should be presented to support the use of the suggested method of dose scaling rather than methods based on drug exposure as the literature suggests that 1) effective drug concentrations in animal models have been found to be predictive of effective concentrations in humans;[3,4] and 2) in vitro and animal pharmacokinetic data can adequately predict human pharmacokinetics.[2,5-7]

Definition of a "new IND" is needed. The majority of companies now have backup and fast following compounds, and the experience from first in human (FIH) with the lead compound, coupled with PK and/or PK/PD modeling and simulation, may be employed on the animal PK data from the same-class backup programs.

Line 48: Addition to paragraph starting on line 48. Preclinical data on the response of putative biomarkers of effect, and of pharmacogenetic targets that may predict drug exposure in human volunteers, may be considered when determining the MRSD.

Lines 50-55: These statements appear to conflict with the proposed method. However, PhRMA agrees and suggests that this approach should be greatly expanded in the document. There is no single prediction method that is reliable for all drugs (including the proposed method). A prudent approach would be to calculate the HED (for pharmacologically active doses in animals, not NOAEL doses) using various allometric and in vitro scaling approaches, and then select the MRSD based on the most scientifically reasonable and conservative estimate.

Line 60-62: With improved analytical techniques providing the possibility of a microdosing approach, unavoidable toxicity is becoming less 'typical'. Toxicity is sometimes encountered when patients rather than healthy subjects are treated because of the desire to provide a seriously ill patient with a predicted therapeutic dose as early as possible.

Lines 62-64: Although the document is not meant to apply to starting doses in patients, the method appears to be in large part based on studies of oncology drugs, which are typically administered to patients instead of healthy subjects.

III. Overview of the Algorithm

Line 68: *Figure 1*: There is no Figure 1 in the document, only a figure in Appendix E.

Lines 78-80: The draft guidance states: "only the NOAEL should be used directly in the algorithm for calculating a MRSD (lines 78-79)." As mentioned above, this comment is quite surprising in light of the potential importance of animal exposure data in selection of starting doses in man. It should be clarified more explicitly why the agency thinks this data should not be a critical component of dose selection for human study.

Lines 84-85: The Draft Guidance states "...this conversion (to human equivalent dose) should be based on the normalization of doses to body surface area (line 84-85)." The guidance also describes the option for using other appropriate scaling factors if more appropriate. However, PhRMA submits that scaling based on body weight is also a commonly used approach. Thus, it

is important that the guidance address more explicitly when this approach would be acceptable. Alternatively, this approach could be listed with equal importance in the guidance as an option for scaling.

Lines 85-88: What is the basis for stating that body surface area conversion is the usual way to approximate equivalent exposure? It has been the experience of PhRMA member companies that measured drug concentrations in the relevant toxicology species are routinely available and provide direct evidence of drug exposure to establish a NOAEL (based on concentration). A discussion of allometric scaling using exposure data from multiple species, which is commonly available information, should be included. It is interesting to note that an FDA scientist has made elegant arguments for the use of allometric scaling and against empirical approaches[8]. Guidance as to when other parameters would be more appropriate and what data should be considered would be helpful.

Lines 96-98: PhRMA suggests modifying this paragraph to indicate that significant toxicity in species other than the species deemed the most appropriate should be considered in the selection of starting doses.

Lines 112-118: The proposed safety factor appears to be empiric and ignores the value of exposure-response data for both pharmacologic and toxicologic effects in choosing a safe dose. In particular, a starting dose is often chosen based on lack of expected pharmacologic effect. Also, the effect of formulation on bioavailability is not mentioned as a source of differences between animals and humans.

Lines 122-127: While the guidance acknowledges that information about a pharmacologic class "may allay concerns and form the basis for reducing the magnitude of the default safety factor and increase.. the MSRD (lines 123-125)", the next line states this information can only apply to a "dose lower than the MRSD (line 125)" can be used as the actual starting dose but this information cannot be used to support a higher potential dose. Again, the guidance should more formally acknowledge the alternative approaches to choosing a starting dose, and not rely in all circumstances on an algorithm.

Line 127: It is ironic that BSA-based scaling is recommended, yet the MRSD's are preferentially expressed in mg/kg. This incongruous approach necessitates much verbiage (such as in abstruse Appendix B that provides negligible clinically useful guidance). If BSA is preferred for scaling, then why is BSA not recommended for individualization across subjects? Specific guidance regarding MSRD calculation for the smallest anticipated subject should be provided in the main guidance.

Lines 133-135: The term 'pharmacologically active dose' is vague; the degree of pharmacological activity associated with this dose should be specified.

Lines 139-140: It would be helpful for FDA to provide the details on this analysis.

IV. Step 1: No Observed Adverse Effect Level (NOAEL) Determination

Lines 147-149: The guidance provides two definitions of NOAEL: Line 148: "the highest dose level that does not produce a significant increase in adverse effects" and, Line 785: "the highest dose tested in an animal species without adverse effects detected". There is a difference between detecting any AEs and detecting a significant increase in AEs, and this should be clarified. PhRMA proposes use of the published definition of NOAEL as "[t]he highest dose at which no statistically significant and/or biologically relevant adverse effect is observed"[9].

Lines 166-174: INDs routinely contain *in vitro* human hepatocyte intrinsic clearance data, and several methods using this data have demonstrated utility in predicting human drug clearance for drugs which are metabolized[7]. We recommend deleting the sentence, "Initial IND submissions... by definition lack human data...," because an initial US IND can be submitted that includes data obtained from first-in-human trials conducted outside the US. It is not clear why systemic exposure cannot be used for setting a safe starting dose in nearly all cases, not just in the example given. For the case given, there is no clear basis for choosing the lowest saturating dose? For example, one could see less than proportional increases in concentrations (e.g. reduction in bioavailability) but still have real increases in concentrations (i.e. when dose is doubled concentrations increase by 50%). Is the lower dose the lowest saturating dose? For another example consider the following table:

Dose (mg/kg)	AUC (ug*hr/mL)
10	10
30	20
100	30

Is the lowest saturating dose 10 mg/kg because further increases are not dose-proportional? Is further investigation required because doses lower than 10 mg/kg may be saturating? Finally, should only AUC be considered when looking at saturation or both Cmax and AUC? The basic message is that by measuring drug concentrations in the appropriate toxicology species, the assumptions inherent in setting the NOAEL in terms of dose are avoided.

This guidance confuses two key issues with respect to pharmacokinetics as applied in toxicology studies and in the prediction of human dose requirement. The first issue concerns exposure (AUC and Cmax) to parent drug and active metabolites at NOAEL dose levels. Utilization of these exposure estimates, after correction for differences in protein binding across species, have been routinely accepted as a valid means of establishing the maximum safe exposure in humans[10]. The second issue is the ability to utilize preclinical in vitro and in vivo data along with human in vitro data to predict human dosing requirements, such that initial exposures in humans will be well below the NOAEL (or pharmacologically active) levels. Progress has been made in this area of prediction[7] with observed human clearance values being within 2-3 fold of predicted values in 70 to 80% of cases. All available data and methods should be used to generate a family of human clearance predictions from which the most scientifically justified first in human dose is selected.

Line 182: The term "responsible investigators" should be defined.

Line 185: PhRMA suggests adding for clarification that an effect could be considered unacceptable based either on severity or clinical significance. There are some clinical findings

in animals, for example, weight loss and vomiting, that are often one of the determinants in assigning a NOAEL. Some additional clarification concerning the role of specific clinical signs in determining the NOAEL would be helpful. Also, perhaps the wording "initial dose" should be modified to the "initial trial" since initial clinical trials may have multiple-dose phases and some adverse effects used to define a NOAEL may only be produced with repeated dosing. In cases where some adverse effects in animals are both dose- and time-dependent, should acute effects be used preferentially in defining the NOAEL for defining the starting clinical dose? Similarly, should the NOAEL be selected from the study of closest duration to the clinical trial, versus studies of longer duration if they are available? This question arises again in the Section VIIB, Decreasing the Safety Factor.

V. Step 2: Human Equivalent Dose (HED) Calculation

Lines 195-201: As noted previously, support for the proposed approach appears to come mainly from studies of oncology drugs. Furthermore, the rationale for using body surface area versus weight does not appear to be well supported by the references provided. Both theory and observation indicate that metabolic clearance is a function of weight$^{0.75}$ (see ref 6). Because systemic exposure is primarily determined by clearance, to achieve an exposure in humans that is equivalent to that at the NOAEL in the relevant animal species it makes sense to scale by weight$^{0.75}$. Additionally, the choice of 0.67 (i.e. BSA) over 0.75 for the exponent appears to be made solely because it is more conservative, not because it is a better predictor. This is supported by the work of Holford and others who indicate that exposure is scaled better by weight$^{0.75}$ than BSA[11]. It would seem more rational to make the best prediction possible and then reduce the starting dose by a factor commensurate with the uncertainty/risk involved rather than to use methods at each step that bias the calculations to lower doses. By recommending the more scientifically valid method of scaling, the need for Appendices A, B and C and much of the discussion in this section would also be eliminated, making the document much easier to follow.

Line 233, Table 1: For clarity, the title of the table should be "Conversion of Animal Doses in mg/kg to Human Equivalent Doses in mg/kg Based on Body Surface Area." Please define km in the table footnote. It seems unnecessary to provide 2 columns of factors that are reciprocals of each other. Likewise, the first column is not directly relevant. Both invite errors if data is taken from the wrong column. By design the constants provided in this table suppress variability due to responses in actual animals, and the likely response in actual humans. Choice of starting and top dose ought to take account of such variability.

Lines 267 – 271: The statement that "toxicity is believed to be related to Cmax" does seem to be a sufficiently rigorous basis for choosing a less conservative calculation.

Line 285: Intrapleural and intraperitoneal are given as examples of "anatomical compartments" from which there is "little subsequent distribution." Intraperitoneal administration is very similar to intravenous, and intrapleural injection would be expected to behave similarly as well.

Lines 288 – 289: What is the basis of this exception and why specify it out of all of the physiological justifications for other scaling factors.

VI. Step 3: Most appropriate species selection

Line 304: The logic supporting 'limited biological cross-species pharmacologic reactivity of the therapeutic' as a basis for species selection is not clear. If the species with the most pharmacological reactivity is not the most sensitive species then it implies that there are other dose-limiting toxicities in the more sensitive species. The sentence at lines 321-323 appears to be the real issue.

VII. Step 4: Application of Safety Factor

Line 337: Addition to VII. Step 4: Application of Safety Factor. Preclinical data on the response of putative biomarkers of effect, and of pharmacogenetic targets that may predict drug exposure in human volunteers, may be considered when determining the MRSD

Lines 338-340: The rationale for the default factor of 10 is not well supported, since it is unclear if this is a "historically accepted value" outside of some specific areas (e.g., cancer, biologics).

Lines 342–350: and sections A and B following. While PhRMA has many concerns about the usefulness of applying this algorithm to all new compounds, these sections are an excellent summary of important considerations in choosing a starting dose and would apply to all approaches.

Line 363: What will be the basis for defining 'severe' toxicity?

Line 369: The lack of prodromal indications could be applied very broadly. Few toxicities have true prodromes, although sensitive biomarkers may exist. The use of specific biomarkers of toxicity, when there is no prodromal toxicity syndrome should be considered in the decision to increase or decrease the safety factor.

Line 377: Reversibility should be examined at multiple points on the dose-response curve, e.g. not consider a toxicity irreversible because of fibrosis induced secondary to very severe effects.

Lines 383-385: Exposure measures other than AUC (e.g. Cmax, Css, time above threshold value) and large interspecies differences in protein binding also may have an impact on the magnitude of the safety factor.

Line 392: Novel therapeutic target. This is not relevant unless the toxicity is mechanism-related.

Lines 401-419: The allowance of smaller safety factors in cases where the NOAEL was determined in a study of longer duration implies that the starting dose in a single-dose escalation study should preferentially be derived based on single-dose animal toxicity studies versus longer term (e.g., 2- or 4-week) studies. However, in some cases this might result in an

inappropriately high initial starting dose. It is presumed that in these cases all of the available data should be rationally evaluated and judgment used in selecting the appropriate study and effect for starting dose determination.

Line 413: Application of Safety Factor, B. Decreasing the Safety Factor. The safe starting dose could be derived differently for human volunteers who have either specific genotypes that indicate substantially different drug exposure, or specific phenotypes based on baseline biomarker characteristics. Patient safety should be monitored using TDM, as necessary, with current practice for PK of drug and metabolite levels as precedent.

VIII. Step 5: Consideration of the Pharmacologically Active Dose (PAD)

Lines 425-433: It is suggested that consideration of the PAD will always be important in choosing a safe starting dose and that this topic should be given greater emphasis in the document. Specifically, it is not clear how the PAD is defined, e.g., EC_{10} or ED_{10}? Also, no guidance is provided on the level of pharmacologic activity that is acceptable for a starting dose.

Lines 521-527: (Appendix A). While the four statements supporting the conversion of NOAEL to HED using the body surface area correction factor are generally recognized, this does not provide a compelling justification for this method as the primary scaling process. Again, the use of alternative methods should be explicitly recognized in this guidance as acceptable and not just in the case that "there is reason to believe that toxic doses do not scale by body surface area (line 760-Appendix E)". For allometric scaling, derived exponents are often used. The guidance does not make it clear whether this would be allowed, or whether 0.67 would always be employed.

References

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