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

RE: Docket No. 02D-0492
Draft Guidance: Estimate the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers

Merck & Co., Inc., is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than $2 billion annually on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. In the course of bringing Merck product candidates through developmental testing and clinical trials, Merck scientists regularly address issues affected by this draft guidance (hereafter referred to as the Guidance). We have extensive experience in deriving a starting dose, based on nonclinical data, for "first in human" clinical trials of new molecular entities in adult healthy volunteers.

We present our general comments first. Thereafter, we present specific comments and recommendations in the order in which the topic first appears in the Guidance. We reference our comments by line number.

General Comments

Merck agrees with the general assumptions expressed in this Guidance that toxicity should be avoided at the initial dose, and all relevant preclinical data should be considered when determining the maximum recommended starting dose (MRSD).

Merck commends the Agency for establishing consistent terminology when discussing the starting dose and for the thoughtful discussion of important factors that must be considered in choosing a starting dose for human studies. Lines 342-350 and Sections A and B that follow, provide an excellent summary of important considerations in choosing a starting dose and should apply to all approaches.

However, we have reservations about using an algorithm as the sole or primary method to select a starting dose. It is overly simplistic to try to reduce the difficult decision to a mathematical equation. The algorithm is useful when other data are lacking, but should not take the place of alternative methods when they generate useful data.

Therefore, the Guidance should be revised to give more weight to the many approaches to select a starting dose for human studies, rather than focusing on one algorithmic approach. There are many approaches to choosing a starting dose for "first in human" studies. These include the approach outlined in the Guidance and variations of this approach, animal pharmacokinetics (PK), allometric scaling to predict pharmacokinetics in man, and pharmacokinetic or pharmacodynamic information from related compounds in a class.[1] While the Guidance acknowledges the important safety factors in choosing a starting dose, it does so only in the context of one algorithmic approach. It would be unfortunate if one method of choosing a starting dose became the standard for all products, when many other approaches are also valid.

The Guidance should be revised to clearly state that alternative approaches may be used in place of the algorithm. For example, the Guidance states that alternative approaches that place "primary emphasis on animal pharmacokinetics and modeling rather than dose (lines 41-42)" are important when choosing a starting dose. We suggest that when animal data are available in sufficient detail to construct a scientifically valid, pharmacokinetic model whose aim is to accurately project an MRSD (line 44-46), an algorithm for choosing a starting dose is less relevant. Likewise, when information from other compounds in a class provides important information on initial clinical dosing, it should be considered most relevant. This is consistent with a widely published conference report, authored in part by FDA staff, that promotes the use of pharmacokinetics, pharmacodynamics, and toxicokinetics in rational drug development.[2]

Lastly, the data concerning starting doses in IND submissions that were reviewed and analyzed by CDER and CBER (lines 138-139), should be shared in a public forum (e.g. an FDA or DIA meeting), while protecting proprietary information, so that the findings undergo peer review and alternative views may be discussed. It is particularly important for scientific colleagues to review the Agency's decisions to focus primarily on body surface area (mg/m^2) as the primary method of scaling, the selection of a safety factor of ~10 (mg/kg), and human dose calculated in mg/kg.

Specific Comments

- **Lines 26-27 and 48-49**: It is not clear that defining an MRSD "regardless of the projected clinical use" is appropriate for all indications, such as those associated with significant morbidity and mortality (e.g., cancers and HIV infection). "Reasonably rapid attainment of phase I trial objectives" is much more important for these indications than for other indications where safety is the primary imperative. Thus, the indication for which the product is being developed should be a factor when determining the starting dose.
- **Lines 33-38**: The text should be revised to clearly limit the scope of this Guidance to "any new drug or biological therapeutic that has *only* been studied in animals, *and not yet studied in humans.*" If human pharmacokinetics data are available, the product should not be subject to this Guidance. Many products are first evaluated in humans in clinical trials

outside the U.S., and hence, a U.S. IND is not required at the time of initial introduction into humans.

- **Lines 40-55 and footnote 2**: These two paragraphs appropriately reflect the role of PK when selecting a starting dose. PK projections should not be the primary basis for selecting the MRSD; PK projections support the decision when paired with preclinical absorption/distribution/metabolism/excretion (ADME) data. The statements in footnote 2 arguing against the use of PK projections also apply to the dose-based algorithm. These issues are best addressed by using conservative assumptions and applying a safety factor regardless of whether the underlying calculations are based on concentration or dose as a measure of exposure.
- **Lines 78-79**: The Agency should clarify why "only the NOAEL should be used directly in the algorithm for calculating a MRSD," and why animal exposure data should not be a critical component of dose selection for first dose in humans.
- **Line 84-85**: The Draft Guidance states, "this conversion should be based on the normalization of doses to body surface area." The Guidance also describes the option for using other scaling factors if more appropriate. We observe that scaling based on body weight is also a commonly used approach. Thus, it is important to address when scaling based on body weight would be acceptable. Scaling based on body weight should be listed as equally important to scaling based on body surface area.
- **Lines 122-127**: While the Guidance acknowledges that information about a pharmacologic class "may allay concerns and form the basis of reducing the magnitude of the default safety factor and increasing the MRSD," line 125 states, "a dose lower than the MRSD can be used as the actual starting dose." We interpret this to mean that pharmacologic class information cannot be used to support a higher dose. This is overly restrictive; sponsors should be permitted to rely on alternative approaches to choosing a starting dose, beyond the algorithm.
- **Line 170**: Differences in plasma protein binding among species also influence the choice of the most sensitive species and should be considered in choosing the most sensitive species.
- **Lines 172-174**: The Guidance appropriately identifies that "when saturation of drug absorption occurs at a dose that produces no toxicity," "the lowest saturating dose, not the highest (non-toxic) dose, should be used for calculating the HED." However, a definition of a saturating dose is arbitrary, and the "lowest saturating dose" may not be the appropriate choice if exposures continue to increase (though not proportionally) with higher doses. In addition, lack of dose proportionality at higher doses in animal species is common, and this set of circumstances is an example of when the approach used in the algorithm (based on NOAELs in mg/kg) is less than optimal. Again, the use of alternative approaches should be explicitly acknowledged in the Guidance.
- **Lines 189-205**: This section implies that BSA scaling is appropriate for between species scaling but body weight is appropriate for scaling human doses between subjects. The Freireich and Schein references do not appear to support the conclusion that scaling based on body surface area (BSA) is generally applicable across all drug classes or to a majority of drug classes, or that it is better than body weight. The primary justification for using BSA (or $BW^{0.67}$) is that it is the most conservative of the approaches generally used. Work by Holford indicates that exposure is better scaled by weight than BSA.[3] Thus, it seems

rational to make the best prediction possible, then reduce the starting dose by a factor commensurate with the risk involved rather than using methods that introduce bias to achieve a lower dose.

- **Line 233, Table 1**: The relevance of the first column is not clear and it is redundant to provide two columns of factors that are reciprocals of each other (*Divide Animal Dose By* and *Multiply Animal Dose By*). The Table as proposed invites errors if data are taken from the wrong column. We recommend that the table be revised as shown in Attachment 1.
- **Lines 288-289**: The Agency should clarify the basis for the following exception to mg/m^2 scaling between species: "Biological products administered intravascularly with $M_r >$ 100,000 daltons."
- **Line 304**: The logic supporting "(3) 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. Lines 321-323 appear to address the same issue. Lines 304 and 321-323 should be combined with a consistent message.
- **Lines 339-340**: The rationale for the default safety factor of 10 is not well supported, since it is unclear if this is a "historically accepted value" for all indications, or only some specific areas (e.g., cancer, biologics).
- **Line 383-385** "*Large variability in doses or AUC levels eliciting effect*": It is not clear that an additional safety factor is needed beyond using the most sensitive species.
- **Lines 521-527** (Appendix A): The rationales for choosing the mg/m^2 normalization are it is widely used and it is conservative. It is further supported by comments such as, "there are no data to suggest a superior method for converting NOAELs," and it is "readily calculated." While all these are true, they do not substantively support the choice of this method as the primary scaling process to select a first dose in humans. We stress that alternative methods should be explicitly recognized in the Guidance as acceptable and not just in the case where "there is reason to believe that toxic doses do not scale by body surface area (line 760-Appendix E)".

In conclusion, Merck commends the Agency for establishing consistent terminology when discussing the starting dose and for the thoughtful discussion of important factors that must be considered in choosing a starting dose for human studies. We respectfully request that the Agency consider the following revisions prior to issuing a final Guidance:

- Sponsors should be permitted to rely on alternative approaches to choosing a starting dose, beyond the algorithm. The Guidance should give more weight to the many approaches to select a starting dose for human studies, rather than focusing on one algorithmic approach.
- The scope of the Guidance should be limited to any new drug or biological therapeutic that has *only* been studied in animals, *and not yet studied in humans.*
- The indication for which the product is being developed should be a factor when determining the starting dose.

- Sponsors should be given the option to use alternative scaling methods, such as body weight. The rationales for choosing mg/m^2 normalization and calculating human dose in mg/kg must be substantiated.
- The rationale for the default safety factor of 10 is not well supported. It is unclear if this is a "historically accepted value" for all indications, or only some therapeutic areas.

We recommend the Guidance be revised to address the points outlined above and welcome the opportunity to meet with you to discuss these issues. In addition, we suggest that the data concerning starting doses in IND submissions that were reviewed and analyzed by the Agency be shared and discussed in a public forum.

Sincerely,

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References

1. Reigner BG, Blesch KS. Estimating the starting dose for entry into humans: principles and practice. *Eur J Clin Pharmacol* 2002; 57:835-45.
2. Peck CC, Barr WH, Benet LZ, Collins J, Desjardins RE, Furst DE, et al. Opportunities for integration of pharmacokinetics, pharmacodynamics, and toxicokinetics in rational drug development. *Clin Pharmacol Ther* 1992; 51:465-73.
3. Holford NHG. A size standard for pharmacokinetics. *Clinical Pharmacokinetics*. 1996;30:329-32.

Attachment 1

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 HED[a] in mg/kg, multiply animal dose by:
Mouse	0.03
Hamster	0.18
Rat	0.16
Ferret	0.19
Guinea pig	0.22
Rabbit	0.32
Dog	0.54
Primates:	--
Monkeys[b]	0.32
Marmoset	0.16
Squirrel monkey	0.19
Baboon	0.54
Micro-pig	0.73
Mini-pig	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] For example, cynomolgus, rhesus, stumptail.