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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; *Guidance for Industry and Reviewers on Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers*

Dear Sir/Madam,

Thank you for the opportunity to review the draft *Guidance for Industry and Reviewers on Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers* (reference the Federal Register notice of 16 February 2003).

Our comments are attached.

Should any clarification of our input be required, please don't hesitate to contact Jenny Peters either by phone (269)-833-8141 or by email (jenny.l.peters@pharmacia.com).

Sincerely,

Pharmacia Corporation

Jenny Peters RPh
Director
Global Regulatory Affairs

02D-0492

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General Comment - While we agree with the appropriateness of the use of surface area in the estimation of safety margins for first-in-human clinical trials, we have concerns over what appears to be a strong emphasis away from approaches based on use of animal pharmacokinetic data. Such an approach in a FDA guidance may have the effect of discouraging efforts aimed at establishing a better scientific understanding of the predictive value of in vitro and in vivo animal models. In particular, this attitude seems to contrast with the spirit of other FDA guidances (e.g., Drug metabolism/drug interaction studies in the drug development process: studies in vitro), in which the collection of basic data regarding the predictivity of experimental (and computational) models is encouraged.

Lines 40–46. Although scope for a pharmacokinetic (PK) approach is allowed, this concept is not developed and an approach based on dose only is favored. This approach appears excessive for a number of reasons. The argument against a PK approach seems to be overstated by setting high standards: "animal data are not available in sufficient detail to construct a scientifically valid, pharmacokinetic model whose aim is to accurately project an MRSD." It can hardly be claimed that the approach based on dose only uses a scientifically valid model, which can accurately predict MRSD. In addition, the approach based on conversion of doses does not protect against violations of the assumptions stated in the footnote (interspecies differences in bioavailability and metabolism, unknown mechanisms of toxicity, toxicity mediated by an unidentified metabolite). ICH M3 recommends the evaluation of toxicokinetic data prior to human clinical trials and encourages the comparison of metabolic pathways in animal 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. There is a danger that putting emphasis almost entirely on a dose-based approach will diminish early-stage ADME studies and the incentive to improve prediction in humans. In any case, particular mention should be made of ADME facets to be considered prior to the first dose in humans. A substantial amount of information concerning interspecies differences is typically available before the first dose in humans, both *in vitro* (metabolic pathways and intrinsic clearance in liver preparations across species, identification of isoenzymes responsible for metabolism and potential for inhibition, fraction unbound across species, etc.) and *in vivo* (pharmacokinetics across species following different administration routes). In particular, interspecies scaling based on a variety of approaches is typically implemented into the program, not only to aid in the design of the first dose trial, but also to support the decision making process. Information obtained from pharmacokinetic and pharmacokinetic-pharmacodynamic evaluations from the nonclinical pharmacology and toxicology studies conducted is especially valuable in designing a FTIH trial. Definition of a "new" IND is needed (INDs supporting first-in-human clinical trials of a new molecular entity?). The majority of companies now have backup and fast following compounds, and the experience from

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 44. In footnote 2, the word "metabolizism" is misspelled in sentence 6.

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.

Line 55. The CPMP Position paper on microdosing could be quoted here as a reference, in order to draw the attention of the pharmaceutical and scientific community to this approach that has been established as a regulatory path in EU.

Paragraph starting on Line 57. "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." With improved analytical techniques providing the possibility of a microdosing approach, unavoidable toxicity is becoming less 'typical'. The fact that toxicity is encountered at an early stage, when patients are used initially in preference to healthy subjects, is often the desire to provide a seriously ill patient with a predicted therapeutic dose as early as possible.

Line 106. Allowance should be made for cases when toxicity is not linked to therapeutic class but say to chemical substituents.

Line 166. 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. Also, in the absence of human data, allometric scaling estimates from animal data are often employed in an effort to predict human PK.

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

Line 185. We suggest to add 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 (See comments on Lines 401-419 below).

Line 198: There is a typographical error in the reference citation. The citation should read Freireich et al (1966), not (1996).

Line 233. 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. Some colleagues, particularly those in the oncology area, that often convert animal and human doses to mg/m^2 were confused by the need for the HED calculation. Perhaps this could be clarified in the text.

Line 234. In risk assessment approaches, a value of 50 kg is often used for a standard human body weight. This factor is more conservative than the assumption of a 60 kg human and provides an additional margin of safety.

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.

Line 325. 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.

Line 352. The many considerations listed for increasing the safety factor seem to imply that safety factors greater than ten may be expected to be more the rule than the exception. Giving some examples of safety factors used by the Agency for some of the toxicities mentioned may be helpful both for the assessor and for industry.

Lines 401-419. Other examples where the use of a smaller safety factor may be appropriate include cases with readily monitorable toxicities (e.g., ALT or AST increases), a shallow dose-response curve, or higher protein binding in human plasma than in animal plasma. 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 (eg, 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 401. VII. Step 4: 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 therapeutic drug monitoring (TDM), as necessary, with current practice for PK of drug and metabolite levels as precedent.

Line 596. Table 3. The kg body weight data for marmosets and squirrel monkeys appear to be incorrect, perhaps missing a decimal point?