Schering-Plough

Integrated Therapeutics Group, Inc
[illegible]
Rockville, MD 20852
[illegible]

March 17, 2003

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

Re: Docket No. 02D-0492; Draft Guidance for Industry and Reviewers on Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers

Dear Sir/Madam:

Schering-Plough has reviewed the Draft Guidance for Industry and Reviewers on Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers, and we offer the following comments for your consideration.

The Guidance describes and argues in favor of a process for deriving a maximum recommended starting dose (MRSD) for first-in-human clinical trials of new molecular entities and *recommends a standardized process by which the MRSD can be selected.* Alternatives are allowed by the flowchart of Appendix E in the Guidance, and the Guidance states 'All of the relevant preclinical data, ..., the full toxicologic profile of the compound, and the pharmacokinetics... should be considered when determining the MRSD.' (lines 50-53). However, notwithstanding the discussion of alternatives, the Guidance as written will clearly discourage use of other methods for choosing the initial dose for human studies of small-molecule new pharmaceutical entities.

Calculations of the MRSD by methods recommended in the Guidance, when applied to compounds that have been studied in humans and animals, show that the methods of the guidance often result in doses that have proven to be appropriate. However, in a number of cases, the methods of the Guidance give an inappropriate MRSD.

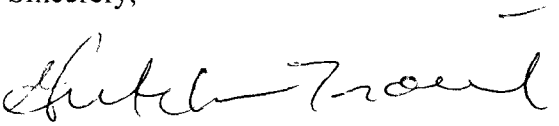
Toxicologic, pharmacokinetic and metabolism studies in animals provide much information that can be used to predict a safe initial dose for human studies. When preclinical studies provide data that give reliable predictive information, that data should be used, with the appropriate justification, to calculate the MRSD. The algorithm (Appendix E) recommended in the Guidance allows an exception to the use of the methods of the Guidance only when '... there is reason to believe that toxic doses do not scale by body surface area.' We believe this overstates the reliability of data and data analysis that are used to support the proposition that body surface scaling is the preferred way to compare doses across species. When data from toxicology, pharmacokinetics and

drug metabolism provide a reasonable basis for choice of MRSD, we believe such data should be usable for this purpose. When such data do not allow a reliable prediction of a safe MRSD, then the methods recommended in the guidance provide a reasonable alternative. As currently written, the Guidance clearly favors the methods of the Guidance over any other data-driven method for choosing MRSD. We believe the decision point in Step 1 in Appendix E should be written as 'Is sufficient data available from preclinical studies to predict the MRSD by a method other than scaling by body surface area?' If the decision point is expressed in this way, data-driven and drug-specific criteria, when sufficient and justified, can be the primary factors in the choice of MRSD. When such data, or their justification, are insufficient, the algorithm of the Guidance will apply.

The Guidance itself cites several deficiencies in the recommended calculation formulae. Scaling by equations different from those of the Guidance is widely used in other disciplines, as cited in Appendix A of the Guidance. In particular, scaling with the exponent 0.75 will, as FDA acknowledges in the Guidance, give better agreement with the data FDA cites as the basis for the Guidance (Freireich et al, 1966). It will also make the calculations more consistent with the methods of other groups, including the Interagency Pharmacokinetics Group. Calculation using an exponent of 0.75 is no more difficult than using exponent 0.67. We believe the Guidance should recommend the scaling exponent that has the most scientific justification

Schering-Plough appreciates the opportunity to comment on this guidance document.

Sincerely,



Gretchen Trout
Director, Regulatory Relations and Policy
Worldwide Regulatory Affairs