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1217 '03 MAR 17 A8:57

March 14, 2003

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

Ref: **Docket No. 02D-0492 - Draft Guidance for Industry and Reviewers on Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers.**

Abbott Laboratories commends the Agency on their efforts to provide guidance to industry on "Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Health Volunteers" published in the Federal Register on January 16, 2003.

We are very pleased to have the opportunity to comment on this draft guidance and thank the Agency for their consideration of our attached comments. Should you have any questions, please contact Ivone Takenaka, Ph.D. at (847) 935-9011 or by FAX at (847) 938-3106.

Sincerely,

for:
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02D-0492 C8

Abbott

March 14, 2003

Comments on Draft Guidance for Industry and Reviewers on Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers

Docket No. 02D-0492

The following comments are provided on behalf of Abbott Laboratories.

GENERAL COMMENTS

Abbott believes the guidance provides a very conservative, valuable and safe approach, generally, in agreement with our approach in estimating dose selection for first in human studies. However, we find the guidance's reliance on observed toxicities, administered doses and algorithmic scaling to be too rigid for the selection of maximum recommended starting dose (MRSD). A pharmacokinetic modeling approach based on Cmax and AUC for drugs with linear pharmacokinetics (PK) is preferred since this also allows a sponsor to predict/model dose escalation and maximum allowable dose. This potential benefit far outweighs the limitation of a PK approach stated in the guidance. Additional preclinical studies to support a PK approach are generally minor and not rate limiting (in vitro metabolism screens, protein binding studies, etc.). Furthermore, as the guidance notes, the application of the safety factor accounts for some of these limitations.

Although it is not the intent of this guidance to address dose escalations, we suggest recommendations as to how to dose escalate should be included in this guidance. In addition, we believe a broader discussion and clarifications on toxicity versus adverse events should also be considered in this guidance.

Finally, Abbott believes the determination of a MRSD is a scientific exercise and many approaches and considerations may be acceptable dependent on the available preclinical data at the time of first in human studies. Furthermore, the guidance ignores a substantial body of data that supports a scientific utilization of modeling data in providing an adjunct to the no observed adverse effect level (NOAEL) in dose estimation. These are relevant and important considerations that should not be excluded from this guidance.

SPECIFIC COMMENTS

III. OVERVIEW OF THE ALGORITHM

The suggested approach to calculating the MRSD algorithm does not address dose escalation or maximum allowable dose. Granted there are many approaches and each therapeutic area may have specific strategies. Focusing the process of determining the MRSD on safety and avoiding addressing dose escalation strategies seems incomplete. We recommend that the Agency address the

acceptability (or not) of dosing above the NOAEL that has been established in animals at any point during the initial Phase I trials if supported by the emerging human data. Since human data supersede animal data, as long as no serious findings are observed, we believe it would be acceptable to escalate further. We would like FDA to state their position on this issue.

Alternative Administration Routes

We appreciate the appropriateness of the guidance recommendations in determining the MRSD when the first in human study plan includes a single route of administration. We would like the Agency to include in the guidance clarifications as to whether MRSDs for each route of administration would be needed when the Phase 1 design employs, for example, both oral and intravenous administration.

IV. STEP 1: NOAEL DETERMINATION

The guidance mentions the maximum tolerated dose (MTD) and the lowest observed adverse effect level (LOAEL) not being generally used as benchmarks for establishing safe starting doses in humans. We disagree with this statement as we believe any one of these parameters, including the no observed effect level (NOEL), could be used for the selection of MRSD, as long as, there is a good understanding of the dose response relationship for the finding. Another scenario, when a NOAEL, for some reason, can not be observed at any dose in early toxicology studies, a starting dose selection can be determined based upon these alternative toxicology parameters, granted that there is sufficient understanding of the mechanisms of toxicity and an adequate safety factor is included.

We would like the Agency to expand the discussion in the guidance in regard to the types of toxicology data needed to determine the NOAEL or MRSD, including, minimum criteria, duration of the study, e.g., whether a two-week study would be acceptable, or a four-week study would be necessary, etc.

V. STEP 2: HUMAN EQUIVALENT DOSE (HED) CALCULATION

In the guidance, the basis for the dose selection scaled to body surface is derived from older data on antineoplastic drugs. We raise two issues regarding the appropriateness of these data. First, there are more recent studies on oncologic agents in the literature that may provide more useful information in comparing human MTDs with animal MTDs. Second, the validity of using antineoplastics as the basis of judgment for all classes of compounds is questionable. Typically, these compounds produce the most tissue disruptive toxicities, generally due to

their mechanism of action, that can be observed even after a single dose. Other classes of agents may perform differently and the toxicities observed tend to be less devastating. We recommend the Agency to take into consideration that similar comparisons be made for scaling dose to body surface area with other therapeutic class agents before generalizing this approach to all small molecular weight new chemical entities in development.

VII. STEP 4: APPLICATION OF SAFETY FACTOR

The guidance discusses the adjustments of the safety factor based on the duration of animal toxicology studies versus the expected exposure in the first in human study, but there is very little discussion on what constitutes the minimal amount of information required; e.g., in a robust data package the safety factors might differ substantially from those of one containing sparse data. Further discussion on incremental adjustments in the safety factor is welcome.

Finally, *in vitro* metabolism data in human and animal cells can be invaluable when used in conjunction with animal PK data to model human exposures. Suggesting that the modeling approach for estimating a starting dose is inappropriate ignores the quality of the science that argues to the contrary. Abbott strongly recommends that a suitable approach to using the *in vivo/in vitro* modeling for dose selection is defined and be included in the guidance.