Comments on the Draft Guidance entitled "Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers"

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Comments by:
Department of Clinical Pharmacology
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February, 2003.

Dear FDA Authors,

Pharmacokinetic scientists within the Clinical Pharmacology Department at Quintiles, Inc., Kansas City, MO, have reviewed and discussed this draft guidance and like to share some of our thinking on this very interesting matter. We appreciate the opportunity to provide feedback on this draft guidance. Overall, this is a well-thought out, well-written regulatory guidance that covers an extremely important, yet less standardized drug development methodology.

I. General Comments

1. NOAEL vs. NOEL

We agree that "No Observed Adverse Effect Levels" (NOAEL) in the most appropriate animal species has been the broadly accepted basis for human starting dose selection. On the other hand, given the emphasis on safety and another commonly acknowledged industry trend to start an initial human dose without, even desirable, pharmacological activity, we suggest that "No Observed Effect Level" (NOEL), which refers to any effect, not just adverse ones, should be considered to provide a more conservative estimation on the starting dose, as opposed to NOAEL.

2. Dose by Factor vs. Pharmacokinetic Interspecies Allometric Scaling

Ther selecting the "Maximum Recommended Starting Dose" (MRSD) delineated in this draft guidance focuses on a dose by factor approach, which is undoubtedly the most commonly adopted methodology by pharmaceutical industry. Nevertheless, it was generally felt that pharmacokinetic interspecies allometric scaling could also be mentioned as an alternative approach to estimate starting dose. Somewhat surprisingly,

the pharmacokinetic interspecies allometric scaling is left out of this draft guidance. In some instances, allometric scaling may provide a less conservative estimation. Furthermore, we believe that pharmacokinetic exposure data (AUC, Cmax) from preclinical pharmacokinetic or toxicokinetic studies (if available) may be a more reliable information compared to the NOAEL dose level. To take advantage of the available animal PK data at the time of dose selection for first-time-in-human study should be encouraged from a scientific as well as regulatory perspective.

3. Non-cytotoxic vs. Cytotoxic Compound

We understood this draft guidance primarily to address the selection of a safe starting dose for first-time-in-human trials in healthy volunteers. As an interesting contrast to the scope of the theme, the majority of the references cited in this draft guidance are studies published in the cytotoxic, anticancer class of therapeutic agents. Evidently, it is inevitable that specific considerations and approaches need to be given to the cytotoxic class of therapeutic agents. Historically, the approach for selection of starting dose varies to a certain extent from non-cytotoxic compound intended for normal healthy subject to cytotoxic drugs intended for patient population in a first-time-in-human trial. In many cases, starting doses for cytotoxic are selected such that administration of pharmacologically inactive doses are minimized. Please clarify in your guidance, if your proposed algorithms also apply to cytotoxic drugs (and patients), or if the cytotoxic compounds are to be addressed in a separate draft guidance.

4. Most appropriate endpoint for MRSD selection

In order to select a starting dose, all available preclinical pharmacology and toxicology data should be evaluated. However, for MRSD selection in case of a single dose first-time in-human Phase I clinical trial the question arises to which extent, 28-day, 3-month or longer exposure toxicology data should be taken into consideration. Based on our experience, there have been cases where the MRSD was selected to be more conservative based on subtle changes observed in long term toxicology studies. This resulted in an increased number of doses required to reach the "maximum tolerated dose" (MTD). Please provide some guidance on how to balance findings in long-term toxicology studies with NOAEL doses obtained from single dose toxicology studies, when single doses are studied in humans.

5. Safety Factors

You are proposing a default safety of 10 for most situations where the MRSD is derived from either the NOAEL or an undesired/unacceptable pharmacological effect dose. Data may be available for preclinical studies that are indicative of an efficacy endpoint. Should a safety factor be considered also on these 'desirable' pharmacological response doses? Is it acceptable to start at doses equal or higher than those that produce a pharmacological response in animals as long as this dose is 1/10 of the NOAEL or an unacceptable pharmacological effect dose?

6. Beyond Starting Dose Selection

Selection of starting dose is the first and foremost step in bridging the late drug discovery/early clinical development, yet starting dose alone is no representative of a successful entry into human, or first-time-in-human clinical trial. With the guidance on selecting the MRSD and default safety factor, there might be situations of a wide window of MRSD and potential MTD. New guidance(s) should be forthcoming in the later stage specifically addressing topics on dose escalation, stopping rules, and establishment of MTD. Thus a complete guidance package on first-time-in-human trial would guide and streamline this critical drug development phase to a great extent.

7. Total Dose in mg vs. Body Weight Normalized Dose in mg/kg

It is not clear from your guidance, if you are proposing to dose all first in man studies based on body weight adjusted doses. While this is a common approach for intravenously administered drug first-time in-human Phase I clinical trials, it is our experience that oral drugs tend to be administered on the same total mg basis across all subjects in lieu of body weight normalized dose. In such instances, a standard human weight or weight range needs to be chosen to compute the total dose.

II. Specific Comments

1. Table 1, header of the second column. We recommend to revise it to read: "To convert dose in mg/kg to dose in mg/ m^2, multiply by km below."

2. Some of the reference body weight and body surface area used in the document may not always be representative of the demographics commonly encountered, e.g. human BW of 60 kg, human BSA of 1.6 m^2 (as opposed to the most commonly use 70 kg, and 1.8 m^2). Some errors were found regarding the two reference body weights for primates in Table 3. Please include literature references cited for all the reference values.

3. The conditions for a decreasing safety factor smaller than 10 would be better exemplified as to what long-duration animal toxicity studies are applicable, for instance, a repeated 28-day multiple dose study or studies with even longer duration.

Conclusion:

We appreciate the opportunity to comment on this draft guidance and look forward to clarifications as pointed out above.

Tanya Russell 2/28/03

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MEMORANDUM

To: **Dr. Robert Osterberg**
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Copy:

From: **Tanya Russell, PhD**

Date: **3/3/2003**

Subject: **Comments to the Draft Guidance "Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers"**

Dear Dr. Osterberg,

Please find attached the compiled comments from the Clinical Pharmacology Department at Quintiles, Inc. The original of these notes has been sent separately by Federal Express.

Best regards,

Tanya Russell

Tanya Russell, PhD
Executive Director, PK/PD