PHARMA BIO-RESEARCH

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Food and Drug Administration
5630 Fishers Lane –
Room 1061- HFA-305,
Rockville, MD, 2085
U.S.A.

Zuidlaren, 14 March 2003
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To whom it may concern:

On behalf of **Pharma Bio-Research Group BV,** I would like to take the opportunity to submit comments on the **Docket No. 02D-0492: *Draft* Guidance for Industry and Reviewers - Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers.**
Our comments are included in a separate attachment. We have also sent these comments by electronic mail.

I also would like to ask advice on the following. At Pharma Bio-Research we are particularly interested in the FDA draft guidance about Estimating the Safe Starting Dose in Clinical Trials. A few weeks before this draft guidance was published, at our institute we had initiated a special project to get more insight in the selection of the first human dose in Phase I studies.
One objective of this project is to get an overview how our clients have selected the first human dose on the basis of toxicology data. A second objective is to study retrospectively for a variety of drug candidates how the original starting dose is related to the MTD or the dose level in humans where the first signs of drug related AEs have been observed. Since we are performing 5 to 10 first-in-man studies per year, we expect to collect these data for approx. 50 compounds over the last 8 years (back to 1995). Among these, there will be compounds which failed in phase I due to (S)AEs and tolerability problems.

Having seen the draft FDA guidance we would be interested to expand this project by taking into account the starting dose that would have been chosen on the basis of the draft guidance. Retrospectively, we can assess how this would have affected the quality of the first-in-man studies, especially the dose escalation efficiency.

We would like to know whether CDER (or CBER) would be willing to give us advice. Do you expect that there could be an interest within the agency for any form of support to or co-operation with Pharma Bio-Research (PBR) for this project? One possibility we could think of is that we share (blinded) data and that we apply the same methodology at PBR as you used for your survey of data to support the draft guideline.

We thank you in advance for your attention in this matter.

Sincerely yours,

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SUBJECT: FDA draft text "Guidance for Industry and reviewers: Estimating the Safe Starting Dose in Clinical trials for Therapeutics in Adult Healthy Volunteers". December 2002 (Docket No. 02D-0492)

INTRODUCTION

Pharma Bio-Research Group B.V. (PBR) is a leading European CRO, located in The Netherlands with facilities in Assen, Zuidlaren and Groningen, and specialised in early clinical drug studies. We have noted the publication of the above draft Guidance and are pleased that the FDA is addressing this important, yet complex, topic. We have taken the liberty to offer some comments (below) to this draft document, subdivided into comments of a general nature and detailed comments on the text.

General comments

1. A choice is being made for a 3-step approach, based on (1) NOAEL in appropriate species, (2) allometric scaling through body surface areas and (3) applying one or more safety factors. We feel that this is a sensible approach, but we would propose to add a scientific rationale in the document, including references showing that the suggested approach provides valid data.
2. The various steps in the suggested approach and the default values used therein are not supported by literature data or in-house evaluations. The basis for choosing scaling based on body surface area seems to be the work of Freireich et al. (1966) and Schein et al. (1970), but these researchers focused on antineoplastic drugs, which form a special category within First-In-Man phase 1 studies.
3. Looking at the references in more detail (13 literature references and 3 ICH Guidelines), it should be noted that 7 of the 13 references deal with anticancer drugs, which, although various principles may be applicable, are not the therapeutics addressed in the present draft. Of the 6 remaining, the most recent one is the well-known article by Boxenbaum and DiLea from 1995. It is surprising that references to more recent literature are missing, for example I. Mahmood and J.D. Balian, Clin. Pharmacokinet. (1999), 36, 1-11; P.L. Bonate and D. Howard, J. Clin. Pharmacol. (2000), 40, 335-340, and the review article by B.G. Reigner and K.S. Blesch, Eur. J. Clin. Pharmacol (2002) 57, 835-845.
4. Various authors, including those cited under 3., have noted that allometric scaling may be a valuable tool retrospectively, but that its potential for prospective purposes must be considered with a strong caveat. In addition, allometric scaling may be less reliable for drugs primarily eliminated via hepatic metabolism. Instead, combinations of approaches are being recommended. We have the impression that the present draft is less cautious with regard to allometric scaling and the use of body surface area. Except for the 2 references addressed under point 2, the other 11 references are not cited in the text. We suggest adding these in order to improve the clarity of the guidance.
5. The document does not indicate the duration of treatment in the studies employed to determine NOAEL; we assume that these are at least 14-day studies, corresponding to the minimal requirements in the ICH M3 guideline.

Comments on the text

Title: Change the term "Safe Starting Dose" into " Maximum Recommended Starting Dose" (reason: it can only be hoped that the starting dose turns out to be safe).
68: Figure 1 is absent in the draft; the process is given in Appendix E.
198: The work of Freireich et al. dates back to 1966; not to 1996.
233: The factor km is introduced here for the first time (in the heading of the second column). Though it is a well-known factor for body surface area scaling, it should be noted that km is also the SI notation for kilometre. We suggest to print this symbol in italics (*km*), as is done at some places in Appendix B
233: Is there a literature reference for the data in this Table?
277: Use mg/m^2 (lower case for m).
590: Give literature reference.

Appendices:
Literature references for the data in the Tables would be helpful.
Appendix E: At this stage in the development of a new drug, how can one assume that the toxic dose will not scale by body surface area?
If one presumes that toxic doses will not scale by body surface area, what is the justification for HED (mg/kg) = NOAEL (mg/kg)?
On the other hand, the suggested bypass provides an easy way to circumvent scaling by body weight: Claim limited confidence in the latter, determine NOAEL and use the normalisation and/or safety factors of your choice.

Glossary:
775 and 777: K (capital) is confusing; should be k and *km*.
787: Definition of NOAEL differs from that given in the text (148, 149).