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

Re: Docket # 02D-0492

We are herewith submitting comments on the document "Draft Guidance for Industry and Reviewers on Estimating the Safe Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers".

I. Comments on the guidance

The draft guidance proposes a process to determine the upper limit of a starting dose (maximum recommended starting dose, MRSD) for clinical trials in adult healthy volunteers. In general, the draft guidance is well written with important points made. It provides a valuable insight into the FDA's experience from many compounds in monitoring human safety, by providing an algorithm for setting a maximum starting dose in the first cohort of a Phase 1 trial with healthy volunteers.

Some texts in the appendix are, however, either confusing or unnecessarily complicated. These are specified in detail below.

Novartis has undertaken a retrospective analysis of its experience and concludes that it confirms the safety of the MRSD using the FDA's algorithm. Many drugs have anticipated pharmacological effects at doses below those indicated as the upper limit of the first dose in human (MRSD) in the guidance. Thus, Novartis believes that pharmacodynamic/biomarker responses should be efficiently explored at doses below the MRSD, if feasible. To foster this activity, we believe the Guidance should indicate that a variety of dose escalation and cohort strategies are acceptable at doses up to the MRSD and are not considered to pose a safety concern. This will provide an excellent opportunity for clinical investigators to test pharmacologically active doses (PAD) predicted from preclinical information - below the MRSD- with efficient escalation to the MRSD.

We acknowledge that initial doses above the MRSD or clinical investigation of doses escalated above the MRSD will be subject to the usual regulatory review. It should be acknowledged in the guidance, however, that the MRSD is anticipated to a fraction of the NOAEL in humans if test species and humans are equally sensitive, and that doses above the test species' NOAEL are often well tolerated in humans. We thus support the position that this guidance is not an appropriate vehicle to discuss doses or escalation above the MRSD, but that such activity must be considered based on specific, individual product profiles and that a variety of methods to accomplish this may be acceptable.

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Concept based comments

Pharmacokinetic modelling is mentioned in the guidance with a number of caveats listed. To the extent that toxicity could be attributed to measured metabolites and parent drug and to the extent that the distribution and accumulation at target organs of toxicity could be included within the physiology based PK model, many of these limitations could be addressed. The biggest drawback in this type of PK/PD relationships currently relates not to predictions of drug pharmacokinetic exposure, but to mechanisms of toxicity and the ability to understand and scale drug toxic responses from small animals to man. Hence while such an approach could be considered, there is still significant uncertainty in the prediction of drug toxicity responses. Such approaches, however, may have application in escalation schemes operating below the MRSD and be useful in exploring pharmacodynamic dose ranges.

Specific comments:

1. Any references for Table 1 on the parameter km? Provide explicit formula for Columns 3 & 4., e.g. conversion factors in Column 4 = km_{animal} / $km_{human(60\ kg)}$.
2. L528: (1) It was not clear how the conversion factors in Table 2 were calculated. It would be better if the factors were calculated based on the mean human (65 kg = (50+80)/2) and mean animal weight ((min+max)/2). (2) Standard conversion factors were not clearly defined in the main text of the draft document. The formula of using these factors to convert to human HED should be stated explicitly in the main text. (3) 3 decimals for the factors in the columns b=0.67 and b=0.75.
3. In Table 4 (p. 20): Give explicit formula for Column E : standard conversion factor = km_{animal} / $km_{human(60\ kg)}$. Column F: provide both extremes. G: the title "±20% range ..." is not quite accurate. Others include: lg human -> 80 kg human; sm human -> 50 kg human; lg animal -> heavy animal; sm animal -> light animal;
4. References are not numbered. Many are not referenced in the text.

Best regards,

Patricia McGovern/fm

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