

Comments from EFPIA on FDA Draft “Guidance for Industry on Exploratory Investigational New Drugs Studies”

[Federal Register: April 14, 2005 (Volume 70, Number 71)]
[Docket No. 2005D-0122]

EFPIA (the European Federation of Pharmaceutical Industries and Associations) represents the research-based pharmaceutical industry operating in Europe. Founded in 1978, its members comprise 29 national pharmaceutical industry associations and 44 leading pharmaceutical companies involved in the research, development and manufacturing of medicinal products in Europe for human use. EFPIA's mission is to promote pharmaceutical research and development and the best conditions for companies to bring to market medicines that improve human health and the quality of life around the world.

The Preclinical Safety expert working group of EFPIA would like to compliment the FDA on the Exploratory IND Guideline which should greatly benefit the industry and enable more rapid evaluation of potential new medicines in man. EFPIA support the general philosophy and overall concept of the guideline and our comments are relatively minor and restricted to the toxicology component of the document.

In Europe, EFPIA have been engaged in very similar discussions with CHMP Safety Working Party to try to identify a reduced preclinical package to support exploratory clinical investigations in man. The main difference in the EFPIA approach is we have recommended conducting toxicology studies in which the doses used are selected to produce an overage of the intended clinical exposure. A quite extensive FTIH database has been collected by EFPIA that provides support for an overage-based approach, details of which are provided in the attachment at the end of this document.

EFPIA's specific comments on the FDA guidelines are:

Lines 342-343 state: 'Repeat dose clinical trials lasting up to 7 days can be supported by a 2-week repeat dose toxicology study in a sensitive species accompanied by toxicokinetic evaluations.'

It would be useful if the rationale for selecting the high dose for the rat 2 week study could be given. We would like to propose that this should normally be a dose the produces some evidence of target organ toxicity, but for compounds of low toxicity a maximum dose of 1000 mg/kg could be used.

Lines 346-347 state: 'If a rodent species is used, additional studies in nonrodents, most often dogs, can be used to confirm that the rodent is an appropriately sensitive species. This confirmation can be approached in a number of ways.'

As mentioned above, discussion are ongoing between EFPIA and the CHMP Safety Working Party to support such exploratory clinical studies by conducting toxicology studies in which the doses used are selected to produce an overage of the intended clinical exposure. A FTIH database has been collected by EFPIA that provides support for an overage-based approach (see attachment for more details). In order to create a degree of harmony between the US and European approaches we would like to propose the following sentence (in red) be inserted (lines 355 - 358).

'Alternatively, the test in the second species could be incorporated as part of an exploratory, dose escalating study culminating in repeated doses equivalent to the rat NOAEL. Another approach could be to conduct an overage-based study in the non-rodent, with doses selected to achieve exposures at least 10-fold higher than the highest human exposure in the proposed clinical study. In all cases the number of repeat administrations in the non-rodent ~~at the rat~~ NOAEL should, at a minimum, be equal to the number of administrations, given with the same schedule, intended clinically.'

Lines 366-370 state: 'If an exploratory IND study is designed to elicit pharmacological effects, each candidate product to be tested should be evaluated for safety pharmacology. Evaluation of the central nervous and respiratory systems can be performed as part the rodent toxicology studies while safety pharmacology for the cardiovascular system can be assessed in the nonrodent species, generally the dog.'

We do not understand why safety pharmacology studies are only required if the clinical study is designed to elicit pharmacological effects. The objective of the clinical study might be around a TK endpoint, e.g. half life, but the dose administered could still achieve exposures that might produce unwanted pharmacological effects. Furthermore, safety pharmacology studies are conducted to identify effects that are not necessarily related to the intended target pharmacology. It would also be useful to provide some guidance on how the dose levels used in the non-rodent CV study should be selected.

Lines 349-351 state: 'The number of animals used in the confirmatory study can be fewer than normally used to attain statistically meaningful comparisons, but of sufficient number to meaningfully identify a toxic response.'

It would be useful to state a minimum number here to avoid any confusion.

Lines 381 - 385 state: 'The maximum clinical dose would be the lowest of the following: (1) $\frac{1}{4}$ of the 2-week NOAEL; (2) $\frac{1}{2}$ of the AUC at the NOAEL in the 2-week rodent study, **or the AUC in the dog at the rat NOAEL**, whichever is lower; or (3) the dose that produces a pharmacological response or at which target modulation is observed in the clinical trial.'

However, in the flow diagram in the attachment, one option (bottom right) for the calculation of clinical stop dose is 'Clinical equivalent of $\frac{1}{2}$ of rat or nonrodent AUC - whichever is lower.' This seems to contradict the text - if the stop dose is based on the non-rodent study should it be the AUC or $\frac{1}{2}$ the AUC?



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