ESTIMATING THE STARTING DOSE IN HUMANS
RECENT DEVELOPMENTS

Rainer Schulz*1 Jean-Pierre Isal*2

Purpose
This abstract presents part of the recent discussion on the methods on how to estimate the maximum recommended starting dose (MRSD) for the first study in humans.

Methods
In 2002, the US FDA published a draft guidance1 proposing an algorithm for deriving the MRSD. This draft guidance is based on the determination of a NOAEL in the most appropriate species, conversion of the NOAEL to a human equivalent dose (HED) based on the normalisation of doses to body surface area and the application of a safety factor (in general 10), i.e. MRSD = HED/10. The NOAEL is defined as the highest dose level that does not produce a clinically or statistically significant increase in adverse effects. Usually, the scaling between species based on body surface, leads to a safer MRSD compared to scaling based on body weight. The principle applied in this guidance is based on the approach of allometric scaling (AS): Dose = aWb, whereby W is weight and a and b are scaling factors. This leads to the following equation for converting animal doses to HED: HED = animal NOAEL x (Wanimal/Whuman)(1-b).

Pharmacokinetically guided approaches
Reigner et al.2 proposed the use of the lowest AUC at the NOAEL in various species as well as the predicted human clearance (CL): Dosehuman = AUC x predicted human clearance. However, this puts the emphasis on the prediction of human clearance. Three different methods were proposed by Mahmood and Green3. Furthermore, four different approaches were looked at to estimate the starting dose based on the predicted clearance in humans.

Limitations of the HED approach
- The choice of a safety factor of 10 is arbitrary and without scientific justification.
- The determination of the appropriate NOAEL can be difficult and depends on a number of key variables, such as duration of treatment, selected doses and species.
- Many assumptions are made in the calculation of the HED based on the normalisation of doses to body surface area.

Limitations of the pharmacokinetically guided approach
The FDA’s position is, that in the majority of cases animal data are not available in sufficient detail to construct a scientifically valid, pharmacokinetic model to accurately project an MRSD.

In addition:
- The difficulties to determine the appropriate NOAEL to select the AUC for further calculations also applies for the PK-guided approach.
- Human bioavailability and metabolism may differ significantly from that in animals.
- PK-guided approaches rely on parent drug in plasma. However, toxicity may be due to a (unknown) metabolite or a mechanism of toxicity not related to the PK of the parent drug.

Conclusion
- The US FDA proposes an empirical approach to estimate an MRSD based on the NOAEL level in an appropriate species, AS to a HED plus application of a safety factor.
- Several methods have been discussed in the recent literature, which need PK data from various animal species to predict human clearance, again using AS, and thereafter estimating an MRSD.
- Both approaches have their own set of limitations.
- If enough PK data from preclinical animal experiments are available, a comparative approach appears to be most careful, i.e. using several methods and critically compare the results.

References