pharmacokinetic (PK) data. Sawyer and Ratain (91) and Kouno et al. (92) discuss the common formulas used to calculate body surface area.

1. NOAEL approach

No Adverse Effect Dose Level (NOAEL) is determined in animal safety studies performed in the most sensitive and relevant animal species. The NOAEL method is commonly used to arrive at a first-in-humans dose. The relevant dose is then reduced by an appropriate safety factor, for example by reducing the dose by a factor of ten. According to FDA's Guidance for Industry, NOAEL is determined as follows. For selecting a starting dose, the following is used, namely, the highest dose level that does not produce a significant increase in adverse effects in comparison to the control group.

2. MABEL approach

Another approach for arriving at a suitable dose for humans is use of the Minimal Anticipated Biological Effect Level (MABEL) approach (93). The MABEL approach provides the dose level leading to a biological effect of interest. The biological effect of interest can be saturation of a drug transport mechanism, stimulation of a cell signaling pathway, or activation of a cell. Calculating MABEL makes use of in vitro and in vivo information available from PK data and PD data.

The concentrations of drug which need to be achieved in the bloodstream of a patient during actual treatment can be estimated by studies with cultured human and animal cells. According to guidance from the EMEA (94) in vitro data with cultured cells can be used to determine, "target binding and receptor occupancy studies *in vitro* in target cells from human and the relevant animal species … concentration–response curves *in vitro* in target cells from human and the relevant animal species and dose/exposure–response *in vivo* in the relevant animal species."

c. Scaling up the drug dose, acquired from animal studies, for use in humans

When an appropriate dose is found from animal studies, that is, by using the NOAEL approach or MABEL approach, an appropriate first dose for use in humans can be calculated using body surface area measurements and by incorporating a safety factor. For

[91] Sawyer M, Ratain MJ. Body surface area as a determinant of pharmacokinetics and drug dosing. *Invest New Drugs*. 2001;19:171–177.

[92] Kouno T, Katsumata N, Mukai H, Ando M, Watanabe T. Standardization of the body surface area (BSA) formula to calculate the dose of anticancer agents in Japan. *Jpn J Clin Oncol*. 2003;33:309–313.

[93] Milton MN, Horvath CJ. The EMEA guideline on first-in-human clinical trials and its impact on pharmaceutical development. *Toxicol Pathol*. 2009;37:363–371.

[94] European Medicines Agency (EMEA). Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (July 2007).