dosing related competitive advantages. The prediction of the therapeutic dose when the drug candidate is going to be used in combination with other drugs is an important consideration for the predictions in oncology (Simeoni et al. 2013). For drug combinations, it is important to examine whether the interaction is additive or synergistic (Schmieder et al. 2013) and to exclude that the additional benefit is due to pharmacokinetic drug–drug interactions, e.g. via CYP inhibition. For compounds where pharmacologically active metabolites are expected to significantly contribute to efficacy, these need to be incorporated quantitatively into the PK/PD models used for the prediction of the human therapeutic dose of the proposed drug candidate.

2.4.4 Estimation of the Therapeutic Window in Human

The therapeutic window is the ratio between the unbound exposure which does not yet show first signs of toxicity and the unbound exposure that is needed for efficacy. A first estimate of the therapeutic window derives from the comparison of the unbound efficacious AUC (from animal PD/efficacy studies) with the unbound AUC in toxicology studies/species which did not elicit adverse effects, i.e. NOAELs. In addition, a range of safety pharmacology studies is performed to estimate plasma concentrations which affect key physiological functions. As conservative estimates, the maximal unbound plasma concentrations are used to evaluate safety risks, i.e. C_{max},u, which are in turn compared to unbound C_{max} concentrations predicted for the highest efficacious dose in humans.

Whereas regulatory safety pharmacology and toxicology studies are being performed prior to entry into human according to authorities' guidelines, potential development candidates are evaluated in non-GLP pilot toxicology studies. They encompass, for instance, 2-week toxicology studies with three dose levels in rodents starting from the dose corresponding to the efficacious unbound AUC with the other two doses representing different multiples thereof. The study design is project and compound specific, depending on prior knowledge from in vivo PK and PD studies, the indication space and the intended patient population.

The selection of the species for the toxicological examination of the compound depends on the metabolic characterisation of the compound, i.e. species similarities in the metabolite pattern with that generated by human hepatocytes. If a human-specific metabolite is not generated in the tox species, it may be synthesised by medicinal chemistry and applied directly in additional study arms. Also important is the achievability of multiples of exposures using microcrystalline material and formulations which can be used later by regulatory toxicology studies. In cases where this poses difficulties, special activities from formulation development are required to progress the project.

The estimation of the therapeutic window also affects the evaluation of potential drug–drug interaction (DDI) risks, depending on whether potential AUC increases would stay within a large therapeutic window or go beyond, thereby putting patients on co-medications at risk. DDI risks may arise from CYP inhibition and/or induction (Prueksaritanont et al. 2013) but also from interactions with