drug–drug interactions (DDI) both as victim and perpetrator when given to patients with indication-specific co-medications and (3) to ultimately allow for a human efficacious dose and dosing schedule which can be formulated and administered in a way that is convenient for clinical use.

Based on the growing understanding of which elements in the concentration–time profile are driving efficacy (the so-called PK/PD driver) and the desired route and scheme of administration, it can be simulated which and how the PK parameters of the lead compound and its analogues need to be optimised in order to turn them into potential drug candidates (Fig. 5). In this phase, it is important to be able to answer key questions such as the following: Which pharmacological IC50 assay variant is most relevant and hence predictive for in vivo efficacy? How much and how long should the unbound plasma concentration stay above this in vitro IC50 to consistently see in vivo efficacy with minimal side-effects? The earlier and the better the team learns to answer these questions, the more they can concentrate their efforts on those parameters which really make a difference rather than getting lost in aspects which are not on the critical path and simply seem easy to be addressed at first sight. The more stringent a team is able to focus, the more rapid it will make progress.

Identification of the elements in the concentration–time profile that are driving efficacy (e.g. AUC, time over IC50, C_{max}, C_{trough}, concentration at a time) requires application of varying the doses and dosing schedules in animal efficacy studies that cover a dose range from full to medium and low/no efficacy. Split-dose studies (e.g. 50 mg/kg vs. 2×25mg/kg) are very useful as the AUC remains the same, but C_{max} and time over IC50 differ. If both schedules are equally efficacious, efficacy is more likely to be driven by AUC, while a higher efficacy of the latter may be suggestive of time over IC50 if this was longer in this schedule. This information can be used to guide PK optimisation depending on what aspect in the plasma concentration–time profile in the current compounds is still suboptimal. If the optimisation goal is to elevate unbound drug concentrations, ADME mechanisms to be optimised are aqueous solubility, intestinal permeability/efflux and/or metabolic clearance, whichever is/are the limiting factor(s) for a given class of compounds (Wang and Urban 2014; Reichel 2014, 2015). Noteworthy, the fraction unbound in plasma or tissues is not an optimisation parameter (Reichel 2009; Smith et al. 2010). If the optimisation goal is to increase the half-life of the LO compounds in order to extent the time over IC50 achievable by a single dose, the parameters to look out for improvements are clearance and volume of distribution. Clearance can be reduced by increasing the metabolic stability of the compounds or reducing the renal or biliary elimination (whichever is the main clearance pathway). The volume of distribution may be increased by making the molecules more lipophilic or basic (Smith et al. 2012).

Focussing on the critical path from a PK point of view means to concentrate on those aspects which really impact the concentration–time course of the LO compounds and their technical DMPK profile in the desired direction. This involves the generation of structure–activity relationships (SAR) and structure–potency relationships (SPR) to explore the chemical space and to elucidate those structural