## 2 Pharmacokinetics in Drug Discovery

In the following, the main tasks and activities of pharmacokinetics during the different phases of drug discovery are described, emphasising the exposure-driven approach of project support with integral PK/PD thinking and considerations. Other DMPK aspects are only touched upon and may be followed up in more detail elsewhere (Kerns and Di 2008; Tsaioun and Kates 2011; Zhang and Surapaneni 2012; Smith et al. 2012; Wang and Urban 2014). Although the chapter has been written with oncology projects in mind, the principles outlined below are also applicable to other indications and small molecule drugs.

### 2.1 Target Validation

For projects that are based on a novel, unprecedented disease hypothesis efforts to validate the new drug target start at the initiation of the project. For these so-called first-in-class projects, there are by definition no tool compounds available, and early evidence for the validity of the target also depends on the availability of suitable animal models which may either involve animals in which the target has been knocked out or significantly attenuated (si-RNA). In these projects, the confidence in the target accumulates throughout the entire drug discovery and development process with the ultimate evidence coming not until the clinical proof-of-concept (PoC) studies.

If the programme is going for a best-in-class approach, there is a high level of confidence in the target, and both tool compounds and relevant animal models are available. A rigorous interpretation of the role of the proposed target in the disease strongly benefits from the availability of exposure data of tool compounds in the animal studies. To assess the compound exposure, plasma samples are being collected from the animals, and, after sample preparation, the compound is quantitated by LCMS/MS analysis. Typically, a crude time course with just a few sampling time points covering the dosing interval suffices. Together with the in vitro data of the fraction unbound in plasma in the animal species, the unbound concentration–time profile in plasma is plotted against a relevant potency parameter, e.g. the unbound IC50 from in vitro tests to see whether the systemic levels reached in the animal study were in the range to cover the target and to elicit the desired effect (Fig. 2). Visualisations of this kind particularly help understanding (1) whether a negative experimental outcome was due to insufficient target exposure or an incomplete understanding of the target and (2) whether a positive outcome of the animal study is in line with the compound exposure at the proposed pharmacological target.