Addressing exposure aspects right from the start of a new project and throughout all phases of the drug discovery process has a significant impact on the selection and optimisation of compounds and the prospect to turn them into viable drug candidates for preclinical and clinical development. The "free drug hypothesis" (Smith et al. 2010) is fundamental to this concept.

The wide acceptance that efficacy (and safety) is not only a result of the potency of a drug at the target (and off-target) protein, but also depends on the exposure of and the engagement with these target proteins has secured pharmacokinetics an immanent role in the drug discovery process. More than a decade since PK representatives have become integral part of drug discovery projects, the attrition rate of projects during clinical development due to PK liabilities went down significantly from originally 40% to less than 10% today (Kennedy 1997; Frank and Hargreaves 2003; Empfield and Leeson 2010; DiMasi et al. 2010, 2013). The attrition at the point of transition to preclinical development is even less allowing viable projects to progress from the discovery to the development phase with a higher probability of success.

This chapter describes how pharmacokinetics supports drug discovery based on an exposure-centred approach by identifying and optimising those PK liabilities which enable both the efficacy and safety of drug candidates and by designing in those ADME properties that result in an adequate PK profile. The role of pharmacokinetics in the different phases of drug discovery is outlined in Fig. 3 which also serves to structure the chapter.

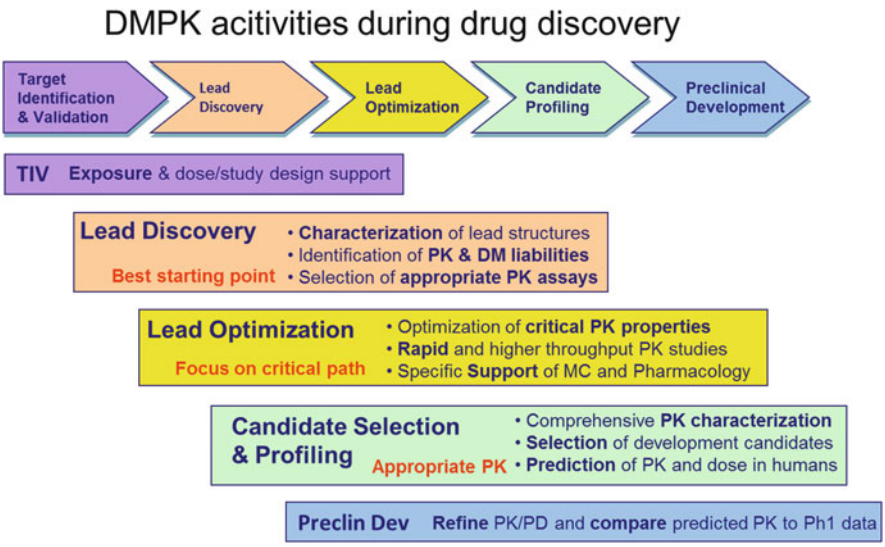

Fig. 3 Overview of the main tasks of DMPK support during the different phases of drug discovery. *TIV* target identification and validation, *PK* pharmacokinetics, *DM* drug metabolism, *MC* medicinal chemistry