translated to anticipate the pharmacologically active plasma concentrations in patients and the human therapeutic dose and dosing schedule which is also based on the prediction of the PK behaviour in human as described herein. The chapter outlines how the level of confidence in the predictions increases with the level of understanding of both the PK and the PK/PD of the new chemical entities (NCE) in relation to the disease hypothesis and the ability to propose safe and efficacious doses and dosing schedules in responsive patient populations. A sound identification of potential drug metabolism and pharmacokinetics (DMPK)-related development risks allows proposing of an effective de-risking strategy for the progression of the project that is able to reduce uncertainties and to increase the probability of success during preclinical and clinical development.

Keywords
ADME · Candidate profiling · Drug discovery · Exposure · Lead generation · Lead optimisation · Pharmacokinetics · PK/PD · Prediction

1 Introduction

Drugs can only exert their desired effects if they are able to bind to the intended target proteins in the body. Although this drug–target engagement is not a guarantee for efficacy, it is a prerequisite for pharmacological effects in the target cells. Efficacy thus is not only dependent on the potency of a drug but also on the exposure of the drug to the pharmacologically active site. Exposure means that the drug must reach the target site at sufficiently high concentrations and for a sufficiently long period of time after it has been administered to the patient. Pharmacokinetics (PK) is the discipline that explores the absorption, distribution, metabolism and excretion (ADME) behaviour of drugs which are the processes that control the kinetics of the concentration–time profile in the blood circulation and the body tissues and organs.

Traditional dose–response concepts are insufficient for the understanding of drug effects if the body and target tissue exposure of the drug is not being considered (Figs. 1 and 2). In a retrospective analysis of Phase II clinical trials, Morgan et al. (2012) extracted three "pillars of survival" for clinical proof-of-concept studies in patients: demonstration of (1) drug–target exposure, (2) drug–target binding and (3) expression of pharmacological activity. The authors concluded that an integrated understanding of the fundamentals of the pharmacokinetic (PK) and pharmacodynamic (PD) principles of a drug is a key success factor with preclinical experimental evidence for at least two of the three pillars significantly enhancing the success rate of drug discovery programmes during clinical development. The conclusions of this analysis have recently been further supported and expanded by a retrospective analysis of AstraZeneca's project portfolio (Cook et al. 2014).