transporter proteins at the level of absorption, distribution or elimination (Giacomini et al. 2010).

While current estimations of the therapeutic window are often static, i.e. based on AUC or C_{max} values, dynamic modelling approaches are used more often as they better reflect the dynamics of the concentration effect relations both for efficacy and safety readouts (Muller and Milton 2012; Parkinson et al. 2013).

2.4.5 Identification DMPK-Related Development Risks

Experience shows that there is hardly any project without issues. The better and the earlier these issues – or risks – are known, the better one can react on them through dedicated de-risking measures. DMPK-related development risks may relate to a number of aspects such as:

1. Safe use in humans, e.g.:
   - Potential for drug–drug interactions as perpetrator and/or as victim, occurrence of toxic or reactive metabolites
   - Nonlinear PK in the therapeutic dose range
   - Potential for large interindividual variability due to involvement of polymorphic drug-metabolising enzymes
   - Drug accumulation due to very long half-life
   - Clearance pathway not compatible with special patient populations, e.g. renal insufficiency

2. Efficacious use in humans, e.g.:
   - Intestinal absorption issues
   - Formulation-related issues
   - CYP induction/autoinduction
   - Potential for large interindividual variability due to involvement of polymorphic drug-metabolising enzymes

3. Difficulty to achieve multiples of exposure of the parent drug and relevant human metabolites in the species used for in vivo toxicology and safety assessment, thereby limiting the exposure range in regulatory toxicology studies and hence complicating or even restraining dose escalations during clinical development

In addition to many other aspects which are not the subject of this chapter, the decision to start preclinical development takes into account the complete ADME and DMPK characterisation of the compound, the anticipated PK behaviour of the compound in humans, the expected therapeutic exposure and predicted dose regimen in patients, the estimated safety margins and the development risks identified. Any risk that has been identified is a strength rather than a weakness of the project as only the issues which have been identified yet allow proposals of appropriate risk mitigation steps at the various phases of preclinical and clinical development.