14 Exploratory Clinical Screening

In addition to the nonclinical evaluation of the drug candidates, revised regulatory guidelines offer various options to perform exploratory clinical studies, which test only low doses with single or short-term multiple administrations in the subtherapeutic to low therapeutic range (Robinson 2008). Because of the low dose, abbreviated preclinical safety testing can be applied, resulting in a significantly lower compound need compared to conventional programs, as the high dose levels to be tested can be distinctly lower than in the standard safety studies (see ICH M3 (R2) 2009). Such early clinical studies can be used to address pharmacokinetic aspects and also drug targeting, e.g., by using imaging technology such as PET (Rowland 2012).

Such exploratory clinical studies ("phase 0") can be helpful, when they support early decision making on the further development of drug candidates before entering full GLP nonclinical safety evaluation (Buchan 2007; Sugiyama and Yamashita 2011). As the required preclinical program does not support a conventional phase 1 clinical study including clinical safety assessment of multiples of the intended therapeutic dose in humans, the nonclinical regulatory GLP safety program has to be completed prior to proceeding into phase 1 clinical studies. Thus, in case of progression of the program, the amount of nonclinical testing is higher than in standard programs. In addition, timelines may be prolonged, when waiting for the results of the phase 0 studies before continuing development (Karara et al. 2010; Yamane et al. 2013).

15 Accessing and Assessing the Acquired Screening Data

In order to make best use of the screening data acquired during early drug development, adequate database and knowledge management tools are required. Whereas single-point measurements of early in vitro pharmacology studies are relatively easily stored in conventional LIMS databases, the more complex multi-endpoint data of in vivo toxicity studies still awaits a broadly accepted database solution. Some companies have developed their own in-house solutions, while others simply rely on the memory of their toxicologists for individual projects results, but there is generally the perception that a quicker and systemic recovery of the acquired data across projects may lead to an improved assessment of early projects even in the situation of scarce data. The European Innovative Medicines Initiative has addressed this need with its eTOX project. The database developed within this project not only developed controlled vocabularies for the mentioned endpoint but also started to share large data sets on toxicity among the participating companies, which will then be accessible for comparison with new drug candidates (Cases et al. 2014).