and drug development. It still causes significant attrition during drug development. Therefore, there is a need for smart selection of drug candidates in drug discovery including screening of important safety endpoints. In the recent years, there was significant progress in computational and in vitro technology allowing in silico assessment as well as high-throughput screening of some endpoints at very early stages of discovery. Despite all this progress, in vivo evaluation of drug candidates is still an important part to safety testing. The chapter provides an overview on the most important areas of nonclinical safety screening during drug discovery of small molecules.

Keywords
Discovery toxicology · Drug discovery · Lead optimization · Nonclinical · Safety pharmacology · Safety screen

1 Introduction

Nonclinical safety and toxicology testing of drug candidates target on assessing the potential adverse effects caused by the drug in relation to its intended use in humans. Hazards related to the compound have to be identified and the potential risks at the intended exposure have to be evaluated in comparison to the potential benefit of the drug. In order to secure a thorough assessment of the nonclinical safety of the drug, multiple aspects have to be covered during the development of a drug.

This includes safety pharmacology, which addresses effects on organ function driven by primary or secondary pharmacology. Mandatory organs to be tested are the central nervous system, the cardiovascular system, and the respiratory system – the so-called core battery. In addition, supplemental testing may be performed addressing other organs, where a specific concern exists toward an impact of the drug on the organ function. Safety pharmacology studies are often performed as stand-alone studies, but they may also be integrated in general toxicity studies, which are best established for anticancer drugs (Authier et al. 2013).

Toxicology testing includes general toxicity after single or repeated administration of the drug including histopathology, the genotoxic and carcinogenic potential of the drug, and the impact on male and female fertility as well as embryo-fetal and postnatal development. In addition, potential local effects of the drug at the administration site, as well as specific aspects like phototoxicity, abuse potential, and immunotoxicity, have to be tested in case of concern. Timing of the safety studies in relation to clinical trials is largely harmonized and concisely described in ICH M3 (R2) (2009). In addition, the occupational safety during production and the environmental safety of the drug have to be assessed.

For the nonclinical safety testing of pharmaceuticals as prerequisite for the start of clinical trials and for marketing application – an area also referred to as regulatory testing – large sets of guidelines exist, which describe testing procedures