Integration of safety pharmacology endpoints in early MTD/DRF studies

Marc Oliver NIEHOFF, Birgit NIGGEMANN, Gerhard F WEINBAUER
Covance Preclinical Services, Germany

While previously the dose selection in early maximum tolerated (MTD) or dose range finding (DRF) studies was mainly based on findings in body weight, clinical observation, food consumption, clinical pathology, and feces evaluation, it can now also comprise evaluation of CNS, respiratory and cardiovascular safety assessment data. This study suggests a feasible study designs and discuss potential advantages and disadvantages considering different pharmacological activities of compounds (small vs large molecule). While classical examinations are still essential for such studies, more comprehensive physical and neurological examinations and spinal reflexes testing as well as neurobehavioral observation (modified Irwin) can be included. Furthermore, quantitative assessment of locomotor activity videos from conscious, freely moving and group housed animals can be taken by video-tracking EthoVision™ XT system and evaluated for distance moved, velocity, duration of movement, time in seconds spent per zone, duration movement in seconds per zone as necessary. Respiratory measurements include blood gas saturation and respiratory rate. For cardiovascular assessment, blood pressure as well as electrocardiogram can be monitored by minimally invasive jacketed external telemetry. Conclusion: In these study designs 4 to 5 days will leave sufficient time to decide about the next dose level of the DRF/MTD phase not only based on “classical” endpoints (e.g. food consumption, clinical observation, feces), but also on CNS, cardiovascular, and respiratory safety pharmacology endpoints. With appropriate bioanalytical methods established, the exposure can also be measured in parallel.