Integrating functional CNS observations into toxicology studies: the PROS!

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Requirement of S7A ICH Safety Pharmacology Guideline

“Central Nervous System (2.7.1)

Effects of the test substance on the central nervous system should be assessed appropriately. Motor activity, behavioral changes, coordination, sensory/motor reflex responses and body temperature should be evaluated. For example, a functional observation battery (FOB) (3), modified Irwin’s (4), or other appropriate test (5) can be used.”
Advantages/Reasons for Inclusion of CNS Endpoints on the Tox Study

• Cost-efficient
• Reduction of animal usage (3Rs)
• Reduced compound requirement – important for compounds expensive or difficult to synthesize
• Pharmacology data can be interpreted within the context of toxicology and toxicokinetic data
• Provides the opportunity for understanding repetitive dosing and under some circumstances the potential reversibility of effects
• Particularly useful for large molecules with long durations of activity
• Can provide large animal CNS data rather than only rodent
Advantages/Reasons For Inclusion (Continued)

• Can include neurological exams to extend the traditional observational data
• No specialized equipment required like on CV and Respiratory assessments so relatively easy to integrate with Tox study
• Can evaluate a broader range of doses due to the toxicology dose selection approach
• Could provide data for both sexes which are not required in the traditional CNS evaluation
Drug Development
Situations Where Inclusion of Assessment on the Tox Study Is Ideal

• Large molecule where the large animal species may be the best choice for characterizing compound activity
• When molecules have a long duration of activity
• Where the CNS is not the site for the mechanism of the compound efficacy
• Where a compound is representative of an earlier SAR where CNS pharmacology was not an issue for drug development
• When a classic rodent CNS study has been conducted and there is a need to better understand the translation of effects to the large animal (additional characterization)