Central Nervous System Safety Pharmacology: Modified Irwin Test

About the author

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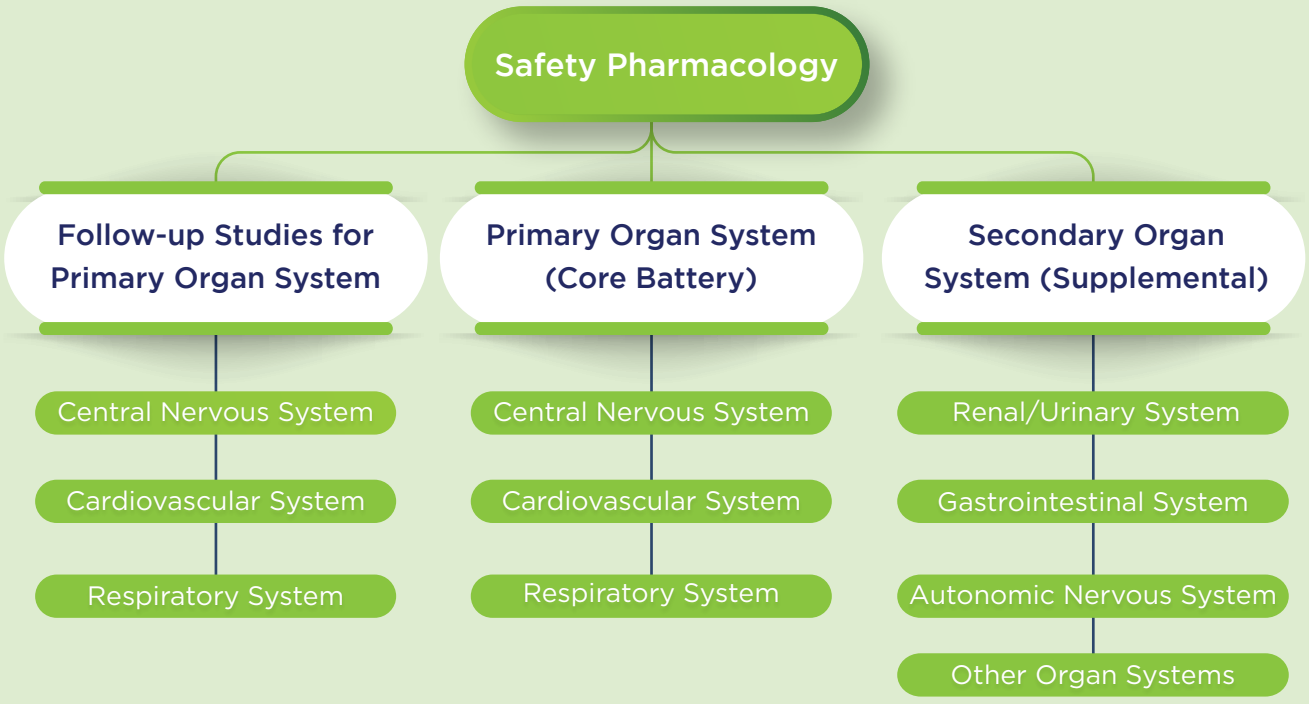
Ms. Pragati Kumari is the Jr. Research Officer at Toxicology Department of JRF. She is involved in conducting of short term and long term studies like, sub-acute, sub-chronic, neurotoxicity, toxicokinetics and safety pharmacology studies and participate in validation of new studies.
She has professional experience of more than 3 years in CRO industries.

1. What is Safety Pharmacology?

According to ICH S7A, safety pharmacology studies are those studies that explore the potential for undesirable pharmacodynamic effects of a chemical on physiological processes in connection to exposure in the therapeutic dose range and above.[1] Safety pharmacology studies generally need to be performed before the first-in-human exposure as part of the IND studies. As per the ICH S7A guidelines, the following studies are recommended based on the physiological system. **(ICH S7A)**



2. Focal Point: Central Nervous System Safety Pharmacology

Investment in the R&D and new drug development is increasing drastically. In 2019, the pharmaceutical sector spent $83 billion on R&D to create new medications. These costs were incurred for a range of activities, including the development and testing of novel medications, the incremental innovation of product expansions, and clinical testing for marketing or safety monitoring. Over the past ten years, there have also been more new medications licensed annually. From 2010 through 2019 (with a peak of 59 in 2018), the Food and Drug Administration (FDA) approved 38 new medications on average, which is 60% more than the preceding decade's average annual approval rate [2].

Survey performed on the results of safety pharmacology studies for CNS indicated that seizures (67% of participants), gait abnormalities (67%), tremors (65%), emesis (56%), sedation (52%), and salivation (47%) were the most common CNS problems encountered during the pre-clinical drug development. While, during the clinical trials mainly in phase I, CNS-related issues like headache (65%), emesis/nausea (60%), fatigue (51%), and dizziness (49%) were noticed [3]. Most of such secondary effects on CNS are easily detected during the pre-clinical CNS safety assessment in the early stage or before clinical studies.

The CNS safety pharmacology can be easily performed at an early stage to identify all such abnormalities and reduce the risk to humans. The distinguishing feature of CNS safety pharmacology from other safety pharmacology is that studies are virtually always conducted in vivo on conscious animals and not in other domains like In vitro approaches. Furthermore, risk evaluation of behavioural data can only be done in a fully awake animal by definition [4].

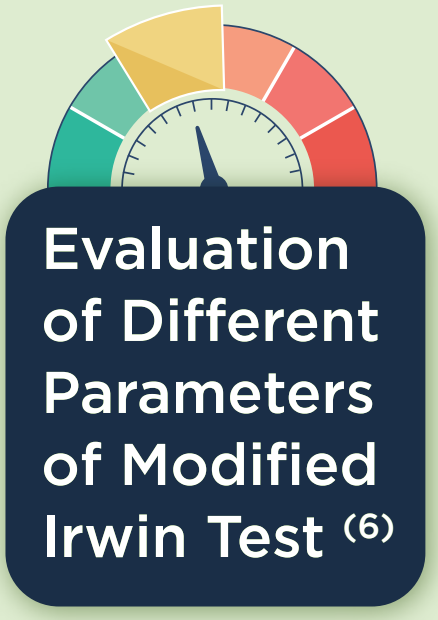
3. What is Modified Irwin Test (MIT)

The application of behavioural approaches in safety pharmacology arose from Irwin's first comprehensive observational procedure for mice, which later served as the foundation for prioritising compounds in the drug development process [5]. MIT is a systematic observational method, that describes the comprehensive assessment and quantification of the behavioural and physiological state of animals and their response to drugs. This method covers various domains of CNS for safety assessment as mentioned below.

Domains include in CNS Safety Pharmacology Study

4. Why do we use Modified Irwin Test (MIT)

- To determine the dose range for CNS reactions, primary behavioural and physiological effects
- To assess the hazards of using the test substances
- Used in the behavioural battery to compare with known chemical liabilities in a drug class
- Determine a test substance's minimal fatal dose
- Forecast possible therapeutic activity and choose doses for later efficacy assessments
- Estimation of the therapeutic index by comparison of doses tested with therapeutic doses



Evaluation of Different Parameters of Modified Irwin Test (6)

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