Nonclinical Abuse Liability/Drug Dependence Testing

Abuse liability potential of an active substance is the propensity of an active substance, as a consequence of its pharmacological or psychological functions, to give rise to a need for repeated doses of the active substance to ‘feel good’ or to avoid ‘feeling bad’. *EMEA guidelines*

**Regulations**

- ICH draft guidance (2008), Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. M3(R2)

**When is Testing Required?**

Nonclinical abuse liability testing should be considered for all CNS active compounds, compounds with novel CNS mechanisms of action and active metabolites of those compounds that circulate in plasma at level 10% or higher than the parent compound. Testing may not be necessary for compounds of the same class as compounds that do not have dependence potential or compounds from a drug class of compounds known to cause dependency but lack abuse liability.

**Assessments**

Covance offers a number of models to help assess the abuse liability of a drug. With Covance’s scientific, internationally recognized expertise in this area, we will consult to develop studies that best meet regulatory expectancies for the compound or drug and provide advice about regulatory interaction.

**Drug Self Administration**

This nonclinical model evaluates whether animals will work to get access to the direct IV injection of the drug. Administering the drug for the rewarding effects that it produces is a direct assessment of the drug’s abuse liability. Amphetamine, morphine, and cocaine are strongly positive in this preclinical test. Drugs that are abused by humans are all scheduled because of the associated abuse liability. Animals are trained to press a lever in an operant chamber to receive the intravenous injection of a training drug (e.g. cocaine), which is perceived as ‘rewarding’.

Following training, the animals undergo testing with the new compound wherein various doses of the test article are substituted for the training drug. Testing is usually performed using a FR10 schedule. Compounds that are self-administered may also be testing under a progressive ratio schedule to determine the ‘breaking-point’ or how hard the animal will work to gain access to the drug. Animals will work at high rates to gain access to highly abused drugs.
Withdrawal/Discontinuation Syndrome (Physical Dependency)

Drug dependence produces continued drug use in order to avoid negative feelings—physical or emotional—that occur when drug administration is stopped. Continued administration of a drug that produces dependence may involve a state of neuro-adaptation and may be associated with the development of tolerance to the pharmacological effect of the drug. Morphine, and even antihypertensives, are examples of drugs that are strongly positive in this test. Identification of withdrawal effects produced by repeated compound administration is not sufficient for drug scheduling/abuse liability.

Animals are initially dosed over a 2–4 weeks with the test article. On discontinuation of dosing the animals are frequently observed for signs of withdrawal. Specific parameters assessed include body weight, food consumption, body temperature, activity, clinical signs and abnormal behaviors.

Drug Discrimination

The drug discrimination model is used to determine the stimulus properties of novel compounds with that of a known class of drugs or to determine if the effects produced by a novel compound can be discriminated from the vehicle.

Animals are trained to associate drug administration prior to the session with a specific operant lever response and to make a different response, usually responding on a second lever, when the vehicle is given prior to the testing session. Food ‘reward’ is used to train animals to make the discrimination between drug and vehicle treatments. Following training the animals are tested to see if novel pre-session treatments are associated with the drug or vehicle training conditions. Drugs that are abused and self-administered in animals are discernable from vehicle treatments since people abuse drugs because of the effect the drug produces.

Expertise

Covance, a recognized leader in the development, optimization and implementation of new techniques for the evaluation of pharmaceutical and chemical products has global experience in performing and interpreting non-clinical behavioral studies. Covance scientists have international reputations in the development of guidelines and methodologies for abuse liability testing. They have extensive experience developing documents for regulatory submission, and experience negotiating testing strategies tailored for individual compounds.

For more information on how Covance can support your drug development efforts, please call us at +1.888.COVANCE or +44.(0)1423.500888.