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STATUS AND DIFFICULTIES OF NEUROSAFETY PHARMACOLOGY RESEARCH

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Before the formation of the ICH S7A technical guidelines, there was no uniform international definition of safety pharmacology, although the United States, Japan and the EU countries all required relevant trial data when accepting new drug registration and clinical research applications. Until 2001, ICH issued S7A research guidelines under the coordination of the three parties. Japan's Ministry of Health, Labor and Welfare formally implemented the Japanese version of the "Guidelines for Safety Pharmacological Experiment Techniques" in 2003. The former State Food and Drug Administration of China also issued the "Technical Guidelines for Drug Safety Pharmacology Studies" in 2014. Since then, safety pharmacology research in China and abroad has gradually become more regulated and received more attention from regulatory agencies in the world. According to the guiding principles of the "Technical Guidelines for Drug Safety Pharmacology Studies" by the former State FDA and "Guidance on Safety Pharmacology Studies for Human Pharmaceuticals (ICH/S7A, 2001)", the assessment methods for neurosafety pharmacology studies can be divided into two major categories: Core Battery and Follow-up/ Supplemental Safety Pharmacology Studies.

The purpose of the core battery test is to investigate the impact of the test drug on the important functions of human body. It is generally believed that organ systems that could endanger human life functions in a short period of time include the central nervous system, the cardiovascular system and the respiratory system. The observation indicators to evaluate the central nervous system in the core battery test generally include: motor function, behavior change, coordination function, sensory/ motor reflex, and body temperature. Its research methods include: Functional Observation Battery (FOB), Irwin Test/modified Irwin Test, Activity Meter Test, Rotarod Test, Convulsive Threshold Test, Barbital Interaction Test, Hot Plate Test, etc. The core battery test demonstrates a direct or indirect measurement that is equally sensitive with drug neurotoxicity and neuropharmacological effects. For example, Porsolt's research shows that antipsychotic drugs can significantly reduce the convulsive threshold, and could also lead to cognitive impairment. The convulsive threshold test is an effective screening for predicting potential cognitive impairment. Some scholars believe that the increase in pain sensitivity caused by drugs will constitute a risk factor for the central nervous system and therefore, it is necessary to include a hot plate test in some studies. According to Frankelin, an American researcher, evaluating the central nervous system in the core battery test is relatively low cost, and can greatly improve the assessment of central nervous system risk.

According to WHO's ATC (Anatomical Therapeutic Chemical) classification, discontinuation of drug use due to safety issues generally relate to 14 different types of toxicity. As of 2016, according to the number of discontinuations and their proportions, toxicity in the first to fourth places are: liver toxicity (60, 21%), cardiovascular toxicity (48, 16%), blood toxicity (31, 11%), neurotoxicity (27, 9%). Rimonabant (Sanofi-Aventis, France), once known as the "magic drug for weight loss", delisted in 2007 due to severe neurotoxicity (causing seizures, anxiety, insomnia, depression, and suicidal tendencies, etc.). Common antibacterial drugs, anti-tumor drugs, local anesthetics, non-steroidal anti-inflammatory drugs, central nervous system stimulants and anti-epileptic drugs may all have certain neurotoxicity. The methods widely used to evaluate the central nervous system are mainly functional combination observation (FOB) and Irwin Test. Currently, the FOB/Irwin Test is most commonly used in rats, followed by mice, monkeys, dogs, and small pigs. More than 60% of the tests are conducted blindly. Reports show that the predictability of Adverse Drug Reactions (ADR) from FOB/Irwin Test to humans is about 19% - 57% (Rat). In order to understand the clinical application results of FOB/Irwin Test, Andy N. Mead conducted research and analysis on the relevant data of 141 small molecule drugs provided by 5 large pharmaceutical companies, including CNS drugs (54 types, accounting for 38%) and non-CNS drugs (87 types, 62%). Animal species for FOB/Irwin Test included Rat (134 species,

95%) and Mouse (7 species, 5%). 109 drugs (77%) showed CNS adverse reactions in clinical phase I, including 49 CNS drugs (45%) and 60 non-CNS drugs (55%). In this study, CNS drugs had 90% probability of showing CNS adverse reactions in clinical phase I, and the probability of non-CNS drugs was 68%. The five most common symptoms of CNS adverse reactions in clinical phase I are as follows (from high incidence of adverse reactions to low): headache, nausea, dizziness, drowsiness/tiredness, and pain.

Prerequisites for additional/supplementary safety pharmacology tests: It is generally believed that, when the results of core battery tests, clinical trials, drug epidemiology, in vivo and in vitro tests, pharmacological effects, chemical structure, and literature reports indicate the test drug may cause potential adverse reactions, appropriate in-depth research or supplementary tests should be conducted to further clarify its characteristics and mechanism. Common follow-up/supplemental safety pharmacology studies include: 1. Cognitive Processes: Passive Avoidance Test, Morris Maze Test , Radial Maze Test, Social Recognition Test, Delayed Alternation Test, etc.; 2. EEG Studies: Quantitative EEG (QEEG), Sleep/Wake Cycle, etc.; 3. Drug Dependence and Abuse: Non-Precipitated Withdrawal Test, Conditioned Place Preference Test, Drug Discrimination, Self-Administration, etc. For example, Bammer's research in 1982 showed that benzodiazepines, anticholinergic drugs, and NMDA antagonists may weaken animal's memory of aversion-type stimuli, resulting in reduced avoidance of previously stimulated environment in the maze test. Therefore, international scholars generally believe that additional/supplementary neurosafety pharmacology tests should cover cognitive abilities (learning, memory, attention), brain function, and the possibility of dependence/abuse. Due to its complexity, there is no fixed standard plan, but there is a stricter requirement, which is, these studies must follow internationally-recognized good scientific standards.

Different from the quantitative/objective methods to test cardiovascular and respiratory system functions, the assessment of central nervous system function in neurosafety pharmacology studies relies to a large extent on many subjective endpoints. At the same time, the research methods have never formed a universal "SOP". Under the framework of the guidelines, the research of each laboratory has a considerable degree of freedom. The current neurosafety pharmacology tests are still mostly core battery test. When the core battery test shows positive result or potential safety risk, additional/supplementary tests are conducted for targeted, scientific, and complete further study. The assessment of CNS is mainly based on subjective test results, and blinding, standardization and automation are of particularly importance. Studies have shown that, if there is a reduction in spontaneous activity in rodents, humans will experience dizziness correspondingly; if analgesia and hypothermia occur in rodents, dogs will show changes in reflex pressure to vagus nerve stimulation, and humans may experience thirst. The most common clinical CNS adverse reactions are not very predictable in pre-clinical trials. Researchers will need to further explore ways to detect more appropriate equivalent symptoms in animals.

In our laboratory's practice of neurosafety pharmacological assessment for many years, we rarely find obvious behavior abnormalities. In individual cases, some drugs caused significant changes in multiple experimental endpoints. For example, in the neurological safety pharmacological test to evaluate anti-type II diabetes drugs on mice, we found that only the low-dose group animals showed reduced number of spontaneous activities within 2 hours after drug dose, and there was statistical difference. Considering there was no significant dose relationship, we concluded it was irrelevant to the test drug. At the same time, a mouse died after pentobarbital sodium injection, and the number of animals in the middle-dose group that fell asleep after pentobarbital sodium injection increased. Considering the sensitivity of individual mouse to pentobarbital sodium, and also considering there was no increased trend in the number of animals falling asleep in the lowand high-dose groups, we concluded it was irrelevant to the test drug. Our laboratory's test results in recent years show that, when the experimental endpoints of neurosafety pharmacology tests had multiple possible positive results, in most cases there were only slight changes or the amount of change was small, or still within the background data range. Most of the significant differences in test results did not reflect a dose-response relationship. We have not found obvious same change trend in certain indicators in a test group or significant/abnormal changes in a single objective indicator. On the one hand, it may be because the test drug has no central effect; on the other hand, it may also be because the current assessment methods lack sensitivity in revealing milder central effect. According to some studies, for neurosafety pharmacology, the risk of type II errors (false negatives) should be reduced as much as possible, and the statistical tests used should be overly sensitive, even if the risk of type I errors (false positives) increases. According to pre-clinical studies, even if over-sensitive statistical data is used, the test drug does not pose a significant safety risk, and it is more likely to be truly risk-free. Therefore, in the development of new drugs, strict control of the conditions of neurosafety pharmacology and experimental conditions remains a major challenge.