Standard for Toxicity Study of Pharmaceuticals

Ministry of Food and Drug Safety Notice No. 2022-18
Partially Amended and Enforced on Mar 2, 2022

Article 1 (Purpose) The purpose of this Notice is to determine the most probable option for a toxicity study of chemicals including pharmaceuticals, etc. submitted according to Articles 31 and 42 of the Pharmaceutical Affairs Act and Subparagraph 4 of Article 9 of the Regulation on Safety of Medicinal Products, etc.

Article 2 (Definitions) The definitions of the terms used in this Notice shall be as follows:

1. “A test animal” refers to a healthy animal in a breed designated for testing. For a rodent, a specific pathogen free (SPF) animal should be used in principle.
2. "Single dose toxicity study" refers to a test designed to qualitatively and quantitatively evaluate short-term toxicity when a single dose of test substance is administered to test animals (including divided administrations within 24 hours).
3. "Repeated dose toxicity study" refers to a test designed to qualitatively and quantitatively evaluate mid- and long-term toxicity by repeatedly administering test substance in test animals.
4. "Reproductive and developmental toxicity study" refers to a test designed to investigate the effect of test substance on reproduction and development of mammals, including fertility and early embryonic development study, pre-and post-natal development study including maternal function, and embryo-fetal developmental study.
5. "Genotoxicity study" refers to a test designed to detect test substance that induces damage to genes or chromosome which is a carrier of genes.
6. “Antigenicity study” refers to a test designed to evaluate whether it causes immunogenicity as test substance works as an antigen of the body.
7. "Immunotoxicity study" refers to a test designed to evaluate abnormal immune response of test substance if there is abnormality in the immune system as a result of a repeated dose toxicity study.
8. "Carcinogenicity study" refers to a test designed to qualitatively and quantitatively evaluate whether cancer (tumor) is caused by administering test substance in a test animal for a long time.
9. "Local toxicity study" refers to a test designed to evaluate irritations that test substance generates in skin or mucous membrane locally, and local toxicity studies are classified into dermal irritation studies and ocular irritation studies.
10. "Local tolerance study" refers to a test designed to evaluate clinical and pathological responses that test substance generates around the injection site in test animals.
11. "Inhalation toxicology study" refers to a test designed to evaluate toxicity caused by inhaling air containing

gases, volatile materials, vapor and aerosol substances in test animals.

12. "Approximate lethal dose" refers to the minimum lethal dose determined based on the life and death and toxicity symptoms of animals observed with different doses.
13. "Maximum tolerated dose" refers to the minimum dose expected to show toxicity symptoms that show decrease or increase of weight gain within 10% compared to control group while not affecting death when test substance is administered in test animals.
14. “Maximum No Effect Level” refers to the highest dose or exposure level of a substance or material that produces no noticeable effect on tested animals.
15. “Lowest Observed Adverse Effect Level” is the lowest dosage level at which chronic exposure to the substance shows adverse effects on tested animals.
16. “No Observed Adverse Effect Level” represents the highest dose or exposure level of a substance or material that produces no noticeable toxic effect on tested animals.
17. "Toxicokinetics" refers to the test designed to calculate pharmacokinetic data [Note 1] to assess systemic exposure of test substance when conducting a toxicity study. The purpose of this study [Note 2] is to evaluate exposure of test substance and correlation between dose level and time lapse in a toxicity study.

Article 3 (Study Item and Test Method) Toxicity study includes single dose toxicity study, repeated dose toxicity study, reproductive and developmental toxicity study, genotoxicity study, antigenicity study, immunotoxicity study, carcinogenicity study, local toxicity study, local tolerance study, single dose inhalation toxicology study, and repeated dose inhalation toxicology, etc. Test methods of each study are described in [Appendix 1-11].

Article 4 (Standard for toxicity Study by Formulation for Combination Drug) (1) A toxicity study for each formulation should be conducted for combination drugs or active ingredients of the combination drugs according to the following subparagraphs, and their test methods should be in accordance with [Appendix 12].

1. For oral dosage forms, injections and infusions, single dose toxicity study, 1-month repeated dose toxicity study, and 3-month repeated dose toxicity study, etc. should be executed.
2. For external preparations, single dose toxicity study, 1-month repeated toxicity study, and local toxicity study, etc. shall be executed.
3. Studies required for formulations other than oral dosage forms, injections, and external preparations are as follows:
   (a) Troches

   A toxicity study should be conducted in accordance with the method for orally-administered preparations, and a mucosal irritation test should be conducted.
   (b) Inhalants

   An Inhalation toxicity study should be conducted in accordance with the provisions of the toxicity

study for injections.

(c) Suppositories for the purpose of systemic absorption

A toxicity study should be conducted in accordance with the method for orally-administered preparations, and a mucosal irritation test should be conducted.

(d) Ophthalmic solutions

1. A single dose toxicity study and a mucosal irritation study should be performed in accordance with toxicity study method for external preparations.

2. In case that an ophthalmic solution can be administered only once, the administration period of the mucosal irritation study for the ophthalmic solution may be conducted once a day for one week.

(e) Toxicity studies of drugs other than troches, inhalants, suppositories for the purpose of systemic absorption, and ophthalmic solutions should be conducted according to methods of which in vivo absorption is most similar to methods applied to humans.

(2) Notwithstanding the provisions of paragraph (1), for combination drugs with the active ingredients of the drug already approved or notified, repeated dose toxicity study data for up to 3 months with one animal species may substitute single dose toxicity study data or repeated dose study data of 1 month and 3 months or more. These data may be waived if any one of the following items is applicable.

1. When the concomitant therapy of individual ingredients in the efficacy and effect, and use and dosage of a single preparation has been approved or notified
2. When the concomitant administration in humans has been sufficiently documented in clinical literatures and the literatures demonstrate there are no significant toxicological concerns associated with the concomitant administration

Article 5 (Supplementary Provisions) (1) In the safety evaluation of pharmaceuticals, etc., new studies may be added or supplemented depending on the toxicity of the test substance. If reasonable safety evaluation for human application may be possible with the toxicity study that has been conducted, the prescribed study method may not be required.

(2) Reliability Investigation of Results of the Review

The Minister of Ministry of Food and Drug Safety (MFDS) can instruct relevant officials or experts designated by the Minister of MFDS to conduct an investigation of the results of the review according to Good Laboratory Practices, if necessary, to confirm the reliability of the results of the toxicity study conducted in accordance with this Notice.

Article 6 (Re-review Period) The Minister of MFDS should review the validity of this Notice every 3 years (by December 31 in every third year) from January 1, 2016 according to the Regulation on Issuance and Management of Instructions and Rules.

ADDENDUM < No. 2017-71, Aug. 30, 2017>

Article 1 (Enforcement Date) This Notice shall take effect on the date of notification.

Article 2 (Application) This Notice shall be applied to the first application for approval (notification) of manufacturing or import (including any change) of medicinal products after this Notice takes effect.

Article 3 (Interim Measures) Notwithstanding Article 2 of the Addenda, toxic studies already underway or completed at the time of enforcement of this Notice may be subject to the provisions of the prior regulation.