

**【Registration of
Proprietary Chinese Medicine】 !**
(Translation from Original Chinese Version)

Product Safety Documents

Technical Guidelines

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Requirements for product safety documents for pCm registration

(A) Introduction

When applying for registration of a proprietary Chinese medicine (pCm), the applicant will be required to provide sufficient documents supporting the safety claims of the product to the Chinese Medicines Board for assessments. The documents shall include the basic and toxicological tests. In addition, the applicant may provide other reference material to support the safety claims of the products, e.g. the published bibliography or monographs, etc.

(B) Brief description of individual tests

Brief descriptions of individual product safety tests are given below. For detailed guidelines of all the tests, the applicant may refer to the content in appendices I to IX.

(1) Heavy metals and toxic element test

(i) Objectives

Heavy metals and toxic element test is required for all categories of pCms to ensure that the content level of heavy metals and toxic element in the pCms are within the permitted level.

(ii) Brief requirements

Heavy metals or toxic elements contained in pCms may be a result of environmental pollution of the raw herbs, from contamination in the preparatory process or simply due to the Chinese herb(s) originally contained heavy metals or toxic elements as ingredients is/are formulated in the preparation. Currently, the permitted level of heavy metals or toxic element is calculated in terms of the total maximum intake per day or per dose. 【For technical guidelines and criteria for limit test for heavy metals and toxic element, please refer to Appendix I (Page iii-iv)】

For preparations that have formulated Chinese herb(s) originally contained heavy metals or toxic elements as ingredients in their prescriptions, the following requirements should be referred:

(a) Established medicines category:

- The quantity of the Chinese herb originally contained heavy metal(s) or toxic element(s) used must strictly adhere to the amount specified in the Pharmacopoeia of the People's Republic of China, etc.
- The applicant must also ensure that the product meets the processing requirements for processing and production, in the course of manufacturing. For instance, processing of Cinnabaris should be in accordance with Chinese medicine bibliography, and should be accepted by the Chinese Medicines Board.

(b) (i) Health-preserving medicines in the non-established medicines category

- As products in this category may be used long term, Chinese herb originally contained heavy metal(s) or toxic element(s) should not, generally be used in these products.

(ii) Single Chinese medicine granules in the non-established medicines category

- It is recommended that no Chinese herb originally contained heavy

metal(s) or toxic element(s) should be used in these products.

(c) New medicines category

- Comprehensive test reports under the new medicines category are required to support the product's efficacy and safety.

(2) Pesticide residues test

(i) Objectives

All pCms must undergo test for pesticide residues to ensure that the content level of pesticide residues falls within the permitted level.

(ii) Brief Requirements

Pesticide residues in pCms refer to the pesticide, its degraded substances and impurities, etc. that remain in the crude drugs. The content level of pesticide residues is measured by the concentration of the pesticide residues in the product.

The pesticide residues test shall be performed in accordance with the following requirements:

- (a) The applicant may choose either the finished product or individual crude drug to test for the 9 types of organochlorine pesticides. If necessary (for instance, when the manufacturing methods of the pCm cause condensation of the remaining pesticides in the finished products), the Chinese Medicines Board may require the test to be conducted on the finished product.
- (b) The applicant is required to submit reports on the test methods and results, and the test results must not exceed the maximum permitted level as specified by the Chinese Medicines Board.

【For the guidelines and specifications for the pesticide residues test, please refer to Appendix II (page v-vi).】

(3) Microbial limit test

(i) Objectives

All pCms must undergo microbial limit test to ensure that the microbial limit is within the specified criteria.

(ii) Brief requirements

The criteria of microbial limit of pCms cover three aspects, namely, “total aerobic count”, “moulds & yeast count” and “the presence of specified bacteria”. The subject product shall be assessed in respect to its dose form and will be considered pass only when it meets all the three criteria set.

【For the guidelines and specifications for microbial limit test, please refer to Appendix III (page vii-xv).】

(4) Acute toxicity test

(i) Objectives

The objective of this test is to provide primary basis for clinical verification and application. Through this test, the toxicity reaction of the test animals and the toxic dose or lethal dose can be determined.

(ii) Brief requirements

The acute toxicity of medicines is usually presented in its median lethal dose (LD₅₀). If the value of median lethal dose is not obtainable with practical measures due to limits on concentration or volume of the product, the acute toxicity can be presented in its maximum tolerable dose (MTD).

(a) Median lethal dose (LD₅₀): This indicates the dosage which can cause death of half of the test animals in single administration.

(b) Maximum tolerable dose (MTD): This indicates the highest dose that the test animals can tolerate without causing death. The dose may be administered to the animals once or multiple times in a day.

【For guidelines and specification for acute toxicity test, please refer to Appendix IV (page xvi)】

(5) Long-term toxicity test

(i) Objectives

The objective of this test is to observe the toxic reaction of the test animals after continuous administration, so as to provide reference for determining a safe dose level.

(ii) Brief requirements

Based on the clinical administration period, set the appropriate test period and administer the product to test animals continuously during this test period. Observe and record the animals' toxicity reactions, including their (first) reactions and seriousness when intoxication occurs, also the development and recovery of their tissue damage and organ dysfunction after the administration is stopped.

【For guidelines of long-term toxicity test, please refer to Appendix V (page xvii)】

(6) Local toxicity test

(i) Objectives

(a) Local-applied medicines include preparations to be used on skin or mucous membrane (e.g. eye preparations, nasal drops, inhalants, buccal preparations, auristillas, rectal and vaginal suppositories, etc.)

(b) The objective of local toxicity test is to examine whether local-applied medicines will cause any irritation or allergic reaction.

(ii) Brief requirement

- (a) Local dermal toxicity Test
This includes skin irritation test and skin sensitivity test.
 - ① Skin Irritation Test
After administering the test medicine to both intact skin and wounded skin, conduct regular observation with the naked eye and histopathologic examinations to evaluate the intensity of the skin irritation.
 - ② Skin sensitivity test
This test is to find out whether the medicine, after being repeatedly applied on animal's skin, will cause the animal's immune system to over-react so that allergic reaction would appear when the skin comes into contact with the medicine again.
- (b) Mucous membrane irritation test
After applying the medicine to certain mucous membrane (according to clinical administration route), observe the irritation reaction of test animals and the recovery process regularly.

【For guidelines of local toxicity test, please refer to appendix VI (page xviii-xxi)】

(7) Mutagenicity test

- (i) Objectives
Mutagenicity refers to the gene mutation caused by effect of the medicines. The objective of this test is to examine whether the pCm has carcinogenicity or reproductive toxicity.

If the Chinese Medicines Board believe or suspect that the product contains substances with mutagenic and carcinogenic effects, the applicant may also be required to provide mutagenicity test report.
- (ii) Brief requirements
The basic principle of mutagenicity test is to expose specific strains of bacteria to the test medicine, and to observe whether mutation happens. Mutagenicity test mainly includes the following three tests:
 - (a) Bacterial reverse mutation test
 - Observe and record the reverse mutation induced by the test medicine in specified microbial species, so as to judge whether it has positive relation with the test medicine.
 - (b) Chromosomal aberration test with mammalian cells in culture.
 - Observe whether the test medicine has induced any aberrance in mammalian cells in culture, and record the occurrence rate so as to judge whether it has positive relation with the test medicine.
 - (c) Micronucleus test with rodents
 - Count the number of cells with micronucleus of the treated animals, so as to judge whether it has positive relation with the medicine.

【For guidelines of mutagenicity test, please refer to Appendix VII (page xxii-xxiii)】

(8) Carcinogenicity test

(i) Objectives

This test is to examine whether the test medicine or its metabolites has carcinogenicity or tumorigenicity.

If the Chinese Medicines Board believe or suspect that the product contains substances with mutagenic and carcinogenic effects, the applicant may be required to provide carcinogenicity test report.

(ii) Brief requirements

Carcinogenicity tests can be divided into two stages: the preliminary study, and the full-scale study:

(a) Preliminary carcinogenicity study

- The objective of preliminary study is to determine the highest dose level that can be used in the full-scale carcinogenicity study.

(b) Full-scale carcinogenicity study

- Observe and record the occurrence rate of tumor in test animals after long-term administration, and assess whether the test medicine has carcinogenic activity on the animals.

【For guidelines on carcinogenicity test, please refer to appendix VIII (page xxiv-xxv).】

(9) Reproductive and development toxicity test

(i) Objectives

This is to examine whether the test medicine has toxic effects on animal's reproductivity and whether it has teratogenic effect on their offspring.

If the Chinese Medicines Board believe or suspect that the product contains substances with reproductive toxicity or mutagenic activities, the applicant may be required to provide reproductive and development toxicity test report.

(ii) Brief requirements

Reproductive and development toxicity test is usually conducted in three stages in accordance with the three periods from before conception to alactation:

(a) General reproductive toxicity test

- The test is conducted prior to and in the early stages of pregnancy to examine whether the product is toxic to the reproductive system of the test animals.

(b) Teratogenicity test

- This is to examine the toxicity of the medicine on the organogenesis of the fetus.

(c) Perinatal toxicity test

- This test is to examine the toxicity of the medicine, and is conducted during perinatal and lactation periods.

【For guidelines on reproductive and development toxicity test, please refer to

(C) Requirements for test laboratories

Laboratories conducting product safety tests for pCms should have met the requirements set by the International Standardization Organizations, i.e., ISO 17025, 『Good Laboratory Practice』 (GLP) or any other laboratories that are accepted by the Chinese Medicines Board. Other municipal Institutes for Drug Control in China that are recognized both by the State Food & Drug Administration (SFDA) and the Chinese Medicines Board will also be accepted.

(D) Summary report of product safety documents

Objectives

The objective of the “summary report of product safety documents” is to give an overall conclusion and a reasonable assessment on the safety of the pCm.

The applicant should draw the conclusion based on the product safety documents submitted.