【Registration of Proprietary Chinese Medicine】!

(Translation from Original Chinese Version)

Product efficacy documents

Technical guidelines
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(A) Introduction

When applying for registration of proprietary Chinese medicine (pCm), applicant will be required to provide sufficient documents to support the product efficacy to the Chinese Medicines Board for assessments. The product efficacy documents include: reference materials on product efficacy, interpretation and principle of formulating a prescription, principal pharmacodynamic studies report, general pharmacological studies report, clinical trial protocol and the summary report, as well as a summary report on all the product efficacy documents. In addition to the above, the applicant may submit other documents in relation to product efficacy, such as published journals or relevant literatures, which may support the product efficacy.

(B) Contents of individual product efficacy document

(1) Reference materials on product efficacy

(i) Objectives
- Reference materials on product efficacy, including reference literature or documentary proofs on long history of use, are to be provided to support the product efficacy.

(ii) Brief requirement
- The requirements for reference materials on product efficacy are listed as follows:

   (a) For pCm that is eligible for transitional registration, the applicant shall submit documentary proofs on history of such use or sales of the pCm.

   (b) For pCm that is not eligible for transitional registration
      (i) Established medicines category
         - For pCm that is formulated in according to an ancient prescription, a modified ancient prescription or pharmacopoeia prescription, or any other prescription from National Drug Standards of the People’s Republic of China, the applicant shall submit copies of relevant materials from Chinese medicines bibliography, Pharmacopoeia or any other National Drug Standards of the People’s Republic of China.

      (ii) Health-preserving medicines in the non-established medicines category
         - The claimed therapeutic functions shall be supported by research studies, or the functions of which have been described in health care literatures compiled by Chinese medicines professionals.

      (iii) Single Chinese medicine granules in the non-established medicines category
         - Copies of relevant materials from Chinese medicines bibliography or Pharmacopoeia shall be submitted.

   (c) New medicines category
      - Reports on product efficacy evaluation and clinical trials, etc. are necessary.
(2) **Interpretation and principle of formulating a prescription**

(i) Objectives

- The efficacy and safety of a pCm is dependant on whether the selected prescription has clearly defined indications or functions, reasonable formulation, correct composition and appropriate dosages. The contents should include the analysis based on the theory of Chinese medicine i.e. the roles of ‘the principal, assistant, adjuvant and guiding drugs’ in the prescription, brief description on the properties, flavors, channel tropism, functions and indications of each drugs, and hence to interpret the efficacy of the pCm.

(ii) Brief requirements

- The interpretation and principle of formulating a prescription shall be written by professionals. The Chinese Medicines Board may, if necessary, require the applicant to provide proof of the professional background of the person who writes this document.

**General requirements on interpretation and principle of formulating a prescription**

[Source]: The provenance of the prescription should be clearly stated, if necessary, the Chinese Medicines Board may require the applicant to produce copies of relevant bibliography for verification. Further elaboration and interpretation may be required if the prescription is an empirical prescription, a modified ancient prescription or a newly developed prescription.

[Ingredients]: Includes name, quantity and processing method of all ingredients of the prescription.

[Usage and Dosage]: Usage and dosage of the preparation shall be specified.

[Functions and indications]: The therapeutic functions and indications of a prescription should be interrelated. Descriptions of the functions should highlight its therapeutic effects and it should be accurate and comprehensive. While the description of indications should include clearly defined syndromes. Generally speaking, the indications should refer mainly to syndromes in Chinese medicine theory and be expressed in academic terminology of Chinese medicine.

[Interpretation]: An analysis and description on functions, indications of the prescription, interaction and compatibility of each ingredient should be given. Interpretation of a prescription can start with the Chinese medicine syndromes – elaboration on etiology, pathogenesis, characteristics of the syndrome, and syndrome differentiation and establishment of therapeutic principles. Then, interaction and compatibility analysis on the basis of the “principal, assistant, adjuvant and guiding ingredients” in the prescription. In the description, the properties, flavours, functions, status and actions of each ingredient in the prescription should be well explained.
(3) **Principal pharmacodynamic studies**

(i) Objectives

- The objective of principal pharmacodynamic study is to obtain preliminary verification on the therapeutic effects of the pCm, and to determine the potency, extent of effects and properties of the pCm, thus providing fundamental but important information for further clinical investigations.

(ii) Brief requirements

- With the theory of Chinese medicine, principal pharmacodynamics studies of pCms make use of modern scientific methods to draw up trial protocols with Chinese medicine characteristics. According to the claimed therapeutic functions and indications of the pCm, appropriate animal disease models and trial methodology are designed to evaluate its therapeutic effects and to provide a scientific basis for these claims.

(iii) Requirements for test laboratories

- Laboratories conducting tests on principal pharmacodynamic studies must have met the requirements set by the International Standardization Organization (i.e. ISO/IEC 17025), Good Laboratory Practice (GLP), or any other laboratories which 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.

(For technical guidelines on principal pharmacodynamic studies, please refer to appendix I (Page iii))

(4) **General pharmacological studies**

(i) Objectives

- The objective of general pharmacological studies is to observe and identify other pharmacological effects in addition to the principal therapeutic actions of the pCm.

(ii) Brief requirements

- In general pharmacological studies, drugs are administered to the test animals to observe its effects on the animals’ nervous system, cardiovascular system as well as respiratory system.

(iii) Requirements for test laboratories

- Laboratories conducting general pharmacological studies must have met the
requirements set by the International Standardization Organization (i.e. ISO/IEC 17025), Good Laboratory Practice (GLP), or any other laboratories which 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.

(For technical guidelines on general pharmacological studies, please refer to appendix II (Page iv))

(5) **Clinical trial protocol and summary report**

**(i) Objectives**
- Clinical trial refers to trial with humans as test participants. Under controlled conditions, the safety and efficacy of the product are examined and assessed in a scientific manner.

**(ii) Brief requirements**
(a) **Phases of clinical trials**
- Clinical trials studies are divided into Phase I, II, III & IV with details described below:

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>A preliminary evaluation on clinical pharmacological effect and safety profile of the test medicine in humans. It is to observe the degree of tolerance in human to the new drug, whenever technically possible, pharmacokinetic studies shall be conducted as to get an indication of the dose schedules that might be used in subsequent studies.</td>
</tr>
<tr>
<td>Phase II</td>
<td>Aim to assess the efficacy and safety of the test medicine, thereby to determine the clinical administration dosage.</td>
</tr>
<tr>
<td>Phase III</td>
<td>It involves multi-center studies and is essential to further evaluate the efficacy and safety of the test medicine.</td>
</tr>
<tr>
<td><strong>Upon approval of the registration</strong></td>
<td></td>
</tr>
<tr>
<td>Phase IV</td>
<td>Post-marketing surveillance is to monitor the efficacy of the product and to detect any adverse reaction after it is available for general use.</td>
</tr>
</tbody>
</table>

(b) **Contents of clinical trial protocol**
- Clinical trial protocol should include:
  - Title, foreword, trial objectives, establishment of trial syndromes, inclusion criteria for study subjects, number of trial subjects needed to achieve the trial objective (based on statistical considerations), trial methodology and proposal, treatments, observation items and their methods, assessment of therapeutic effects, observations, assessment and reports on adverse reaction or events, criteria for trial subject to terminate the trial, methods of data processing and analyzing, design of the case report form, investigation of compliance, participant’s informed consent form, qualification and responsibility of investigators, qualification and responsibility of monitors, management of trial drugs, etc.
(c) Contents of the summary report of clinical trials
- The summary report shall summaries and analysis the information collected in the trials.

- When the trials are finished, each trial center shall compile and submit their own trial reports, and the management in charge of the overall clinical trial shall then compile a summary report summarising the trial reports submitted by each center.

- The summary report shall include: title, summary, objectives, case selection, trial methodology, assessment on therapeutic effects, trial results, typical cases, analysis and explanation on withdrawn cases or of adverse events, discussion and conclusions on therapeutic effects and safety. In addition, names, professions and titles of the protocol designer, investigators of the clinical trial and the principal investigator(s) shall also be included.

- In the discussion section of the summary report, the conclusions shall cover the functions (or indications), applicable scope, administration regimen, treatment period, therapeutic effect, safety, adverse reaction, contraindications and other caution information of the new drug based on the results of the trial.

(d) Documents to be submitted upon application
- Upon application, the applicant shall submit: the clinical trial protocol of all phases, approval letter from the ethics committee, and the summary report of phases I, II & III of the clinical trial. Within 2 years after the registration, the applicant shall submit the summary report on phase IV of the clinical trial.

(iii) Requirements for Clinical Trial centres
- Centres conducting the clinical trials for pCms must have met the requirements of “Good Clinical Practice for proprietary Chinese medicines” (GCP) or other equivalent standards. Other clinical trial centers in China that are recognized both by the State Food & Drug Administration (SFDA) and the Chinese Medicines Board will also be accepted.

(For technical guidelines on clinical trials, please refer to appendix III (page v - viii))

(6) Summary report on product efficacy documents

(i) Objectives
- The purpose of the summary report on product efficacy documents is to give an overall conclusion and a reasonable assessment of product efficacy.

(ii) Brief requirements
- The applicant shall organize and compile a summary on the product efficacy documents where upon he/she shall present a reasonable and well-founded evaluation and conclusion on the efficacy of the pCm.