【Registration of Proprietary Chinese Medicine】

(Translation from Original Chinese Version)

Product quality documents

Technical guidelines
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(A) Introduction
When applying for the registration of a proprietary Chinese medicine (pCm), applicants are required to provide all the prescribed product quality documents to the Chinese Medicines Board for assessments. These documents include:
- Manufacturing method;
- Physicochemical properties of crude drugs of the pCm;
- Product specification, methods and certificate of analysis; and
- Stability test report

(B) Contents of individual product quality document

(1) Manufacturing method
(i) Objectives
The manufacturing method has a close relationship with the product quality. In the course of manufacturing, each step in the process, the quality and quantity of all ingredients used, as well as temperature, humidity, etc., all these will affect the quality, safety and efficacy of the finished products. Hence, the manufacturing method of pCm has major significance to the quality of the product.

(ii) Content requirement
The following information should be submitted for assessment:

【Manufacturing method】
Briefly describe the manufacturing method according to each preparation step, processing procedure for each raw herb, as well as names and quantities of all excipients used in the processes. For those procedures that may affect the quality of the pCm, the technical controls shall be specified e.g. number of hours and times required to boil the Chinese herbs. For instance, some examples are given as below:

1. Longdan Xiegan Wan: Crush all Chinese herbs into powder; sift, mixing thoroughly, make pills with water and dry.

2. Niuhuang Jeidu Pian: Levigate or pulverize realgar to very fine powder, pulverize radix et rhizoma rhei to fine powder, triturate calculus bovis and borneol to fine powder; boil radix scutellariae together with other four herbs in water twice, two hours each time, and then mix the decoction and boil again, then filter. Evaporate the filtrate to a thick extract, add the powder of radix et rhizoma Rhei and realgar, make granules and dry. Add the powder of calculus bovis and borneol, mix thoroughly, compress into tablets.

(2) Physicochemical properties of crude drugs
(i) Objectives
This is to accurately identify and assure the quality of the crude drugs in the pCm, as to provide evidences that the crude drugs have conformed to the required standards.
(ii) Content requirements

a) The crude drug(s) of a pCm that fall into any of the following four groups, the applicant shall submit relevant literatures or scientific research reports detailing the physicochemical properties of the crude drug:
   1. A newly-discovered Chinese herb
   2. A new medicinal part of a Chinese herb
   3. An active group extracted from Chinese herb
   4. A set of active groups extracted from a compound prescription

The specific content may include the following four aspects or other applicable tests:

1. **Description:**
   - This information shall include description on shape, size, color, texture, section surface, smell, etc. of all raw/crude herbs.

2. **Identification:**
   - Appropriate identification methods should be adopted in according to the physicochemical properties of the crude drugs. The identification methods should enable investigators to analyze and identify the chemical compositions of the crude drugs.
   - Identification methods may include microscopic identification, general physicochemical identification, chromatography and spectrometry as well as other applicable methods.

   i. **Microscopic identification:** to obtain information from observation of internal structure of the crude plant material through optical microscope or electron microscope, e.g. amylum form, crystal shape.

   ii. **General physicochemical identification:** To identify the crude herbs and their chemical compositions using general physicochemical analytical methods.

   iii. **Chromatography:** Using various chromatography methods to analyze crude herbs and their chemical compositions, chromatogram can be generated and based on which information on identification and assay can then be obtained. Commonly used chromatography includes thin-layer chromatography (TLC), gas chromatography (GC) and high performance liquid chromatography (HPLC).

   iv. **Spectrometry:** Using various spectrometry methods to analyze crude herbs and their chemical compositions, spectrum can be generated and based on which information on identification and assay can then be obtained (for example: ultraviolet and visible absorption spectrometry, infra-red spectrometry, etc.).
- For chromatography or spectrometry, appropriate reference substances or reference herbs should be used for comparison wherever possible.

3. Inspection:

- To determine type and quantity of foreign matters in crude drugs. The manufacturer shall establish an acceptable specification for the amount of foreign matters found on the herbs, and provide appropriate supporting references for such specification. Inspection of crude herbs shall include the following three items:

  i. **Determination of foreign matters**: To determine organic foreign matters (e.g. adulteration with other herbs) and inorganic foreign matters (e.g. sand and soil) mixed in the herbs. These foreign matters can be observed with naked eyes or magnifying glass, and can be picked out and counted to determine its quantity.

  ii. **Determination of ash**: To determine ash or acid insoluble ash in herbs.

  iii. **Determination of water**: To determine the water content in herbs.

4. Assay:

- The content level of active ingredients or marker compound of a herb is a key indicator of its quality. An assay can be conducted by using chromatography, spectrometry or general physicochemical methods. If the analytical methods developed by the laboratory, the applicant will be required to explain the methodology involved and to provide supporting documents, which shall include method validation and other relevant information.

- The manufacturer shall establish the permitted content level of active ingredient and marker compound in assayed items, and shall provide the relevant supporting document.

- In addition to adopting appropriate test methods for the above assayed items, the applicant shall also provide relevant information on testing conditions, selection criteria and the test report.

b) If the crude herbs of the pCm do not fall into any of the four types as mentioned above in (a), the applicant is generally required to submit literatures and articles on the physicochemical properties of the crude herb, and specify the sources of the relating documents (for instance, copy of the monograph recorded in the Pharmacopoeia of the People’s Republic of China containing description, identification, inspection, assay of the herb), without having to submit the relevant test reports.
(3) **Product specification, methods and certificate of analysis**

(i) **Objectives**
The product specification of pCm is the quality criterion set by the manufacturer for their finished products. Test methods shall be set as per general test specified in the product specification, and the certificate of analysis shall reflect the quality. The purpose of these requirements is to ensure that the pCm has consistent and stable quality and has met the standards set.

(ii) **Contents requirements**

**【Product specification】**
The product specification shall be established by the manufacturer and submitted to the Chinese Medicines Board for review, and it shall include the following items or other applicable items:

a) **Description:**
   - This refers to color, shape, smell, etc. of the finished products.

b) **Identification:**
   - When selecting identification parameters of the finished products, priority should be given to the active constituent, precious constituent and constituent with toxic effects, etc. in the prescription.
   - Identification methods may include microscopic identification, general physicochemical identification, spectrometry and chromatography etc.
   - For chromatography or spectrometry, appropriate reference substances or herbs should be used for comparison wherever possible. Specific, sensitive and reproducible identification method(s) should be adopted. The basis of the method(s), the application of spectrum and data should be well explained.

c) **Assay:**
   - When establishing assay parameters, priority should be given to the chemical composition of the principal, precious constituent and constituent with toxic effects, etc. in the prescription.
   - If necessary, the known chemical composition of other constituent or characteristic constituent in the prescription that can reflect the product quality may also be taken as the assay parameters. If it is technically impossible to conduct an assay for any single chemical constituent, content level of all constituents or that of extracts may also be taken.
   - Assay methods for known or characteristic constituent of the finished product can be established by referring to relevant literatures or be developed by the applicant/manufacture’s own research. For the methods developed by independent research,
the applicant will be required to state the methodology involved, and to provide relevant reference documents, in which the method validation should be included. Should the finished product contain any constituent with toxic effect, the (maximum) permitted quantity of the toxic constituent should be clearly specified.

d) **Inspection:**

- The applicant shall list all foreign matters in the finished products. Content levels of foreign heavy metals and toxic elements, pesticide residues, microorganisms, etc., should be clearly specified.

- For each dose forms of the finished products, the applicant shall adopt corresponding general tests, and shall state clearly the product specifications of these tests. For the general tests for various dose forms of pCms, please refer to appendix I (page ii).

**【Test methods】**

The applicant shall establish relevant test methods for each test specified in “product specification”, and shall provide relevant basis (including test conditions and selection criteria) for these methods. The prime concern of the test methods adopted shall accurately identify the finished products and reflect its quality.

**【Test report】**

All tests referred to in the test report shall be conducted according to the “test methods”, and results shall be in conformity with requirements specified in “product specification”.

(4) **Accelerated stability test**

(i) **Objectives**

The objective of accelerated stability test is to establish the shelf life of the product.

(ii) **Contents requirements**

Accelerated stability test refers to the regular assessment on changes in product quality to establish the stability and shelf life of the product when it is kept in a specified temperature and humidity storage conditions (i.e., with temperature at 37°C-40°C and relative humidity at 75±5%). Depending on the dose forms, the shelf life deduced from this test shall not be more than 2 years.

[For test methods and determination items of various dose forms, please refer to appendix II (page iii).]
(5) **Real-Time stability test**

(i) **Objectives:**
It is to provide a sound basis for establishing the shelf life of the product and to ensure the safety and efficacy of clinical application of the product within its shelf life.

(ii) **Content requirements:**
Real-time stability test refers to the regular assessment on changes in product quality to determine the stability and shelf life of the product when it is in its actual sales packaging kept in ambient conditions (i.e. with temperature at 25°C ±2°C and relative humidity at 60%±5%).

[For test methods and determination items of various dose forms, please refer to appendix II (page ii).]

(6) **General stability test**

(i) **Objectives:**
It is to re-assure the quality of the product remains stable within the claimed self life by conducting stability assessment on the retained samples.

(ii) **Applicable Products:**
This applies to all pCms of Established and Non-established medicines categories that have been manufactured or sold in Hong Kong before the deadline for application of transitional registration.

(iii) **Content Requirements:**
For general stability test, the product in its actual sales packaging is being kept under room temperature or proposed storage conditions of the product at the manufacturer. Regular inspections and tests are conducted so as to determine the expiration period of the drug.

[For test methods and determination items of various dose forms, please refer to appendix II (page iii-vi).]
(C) Requirements for test laboratories

- Laboratories conducting tests on the physiochemical properties of crude drugs and product specification for pCms must have met the requirements set by the International Standardization Organization, i.e. ISO/IEC 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 can also be accepted.

- For laboratories which have been granted ISO/IEC 17025 accreditation of the three basic tests, namely:
  1. Heavy metals and toxic element test;
  2. Pesticide residues test; and
  3. Microbial limit test,

the Chinese Medicines Board will also accept certificates of analysis and stability test reports issued by these laboratories.

- For stability tests, at least the first batch of product should be conducted in test laboratories that have met the above requirements. The remaining batch(es) can be conducted by the manufacturer of the product, and that manufacturer should have met the requirements of “Good Manufacturing Practice” (GMP), including both the manufacturing process and quality control of pCms.