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Traditional Chinese medicine — General requirements for the manufacturing process of natural products

Médecine traditionnelle chinoise — Exigences générales relatives au procédé de fabrication des produits naturels

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Foreword

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This document was prepared by Technical Committee ISO/TC 249, *Traditional Chinese medicine*.

Introduction

Natural products used in traditional Chinese medicine (TCM) are manufactured from materials of natural origin, the quality of which is varied according to geographical, climatic and seasonal conditions. For quality assurance of final products, quality evaluation on starting materials for natural products used in TCM is essential. On the other hand, it is also important to handle these natural materials appropriately and to control manufacturing processes for natural products used in TCM.

The management of manufacturing processes under good manufacturing practice (GMP) is indispensable to ensure quality of medicinal products. International GMP was issued by World Health Organization (WHO) in 1967, and a number of regional and international GMPs have subsequently been established. Recently, Pharmaceutical Inspection Convention (PIC)/Pharmaceutical Inspection Cooperation Scheme (PIC/S) has been widely applied around the world. At present, two-thirds of the member bodies of ISO/TC 249 are affiliated with PIC/S and some other countries are waiting for review of their applications.

These general GMPs were extensively applied to different fields and complimented with special supplements for herbal medicines in some countries and organizations. However, these herbal GMPs are focusing on European herbal medicines, but not covering those in the East Asian regions such as China, Japan and Korea where traditional medicines are used.

The current herbal GMPs of WHO, EU or PIC/S are mainly based on single herbal products, and the products consisting of more than one herbs were stipulated as special cases. However, multi-herbal products are more common than single-herbal products in the East Asian regions. In addition, raw materials in herbal GMPs of WHO, EU or PIC/S are only exclusive for plant origin, while traditional medicines in East Asia also include animal and mineral materials. In order to use correct materials, it is important to identify the starting materials not only by physical/chemical examinations but also by perceptive identification by well-trained experts. However, the requirement for experts on natural materials are not described in these international herbal GMPs. For a better safety and quality control of TCM products, conventional GMPs for the manufacturing of herbal medicines are in need of improving by this proposed standard.

Therefore, based on Chinese, Japanese and Korean herbal GMPs, and with reference to international GMPs, this document specifies general requirements for manufacturing processes that are particularly applied to natural products used in TCM. Implementation of this document with conventional GMPs for general pharmaceutical products would make it possible for manufacturers to ensure the safety and quality of natural products used in TCM, and at the same time prevent people in countries where such products are used from health hazards caused by poor quality products as well as improving their health. It will allow people to enjoy the benefits of natural products used in TCM for treatments of diseases as well as promoting health. This document will also allow non-PIC/S member countries to request quality assurance of the products to manufacturers and manufacturing countries with reference to this document. Finally, this document will make it possible to complement and/or amend WHO, EU and PIC/S herbal GMPs.

Traditional Chinese medicine — General requirements for the manufacturing process of natural products

1 Scope

This document specifies the general requirements for manufacturing processes to ensure the quality of finished products used in traditional Chinese medicine (TCM). This document covers premises, documentation, personnel, training, manufacturing control and quality control. This document applies to the manufacturing of natural products used in and as TCM.

This document does not conflict with general pharmaceutical good manufacturing practices (GMPs).

This document applies to all materials of natural origin: medicinal plants, medicinal animals, medicinal minerals, crude drugs or crude drug preparations.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at http://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

NOTE Traditional Chinese medicines include various types of items. The same material can be classified in different categories (e.g. a powdered plant material can be both a crude herbal drug and a crude herbal drug preparation or, in a packed form, a traditional Chinese medicinal product).

3.1
active ingredient
crude drug(s) or the crude drug preparation(s) of a traditional Chinese medicine(s)

[SOURCE: WHO guidelines on good manufacturing practices (GMP) for herbal medicines, modified]

3.2
constituent of known therapeutic activity
substance or group of substances that is chemically defined and known to contribute to the therapeutic activity of a crude drug or of a preparation

[SOURCE: WHO guidelines on good manufacturing practices (GMP) for herbal medicines, modified]

3.3
marker substance
chemically defined constituent of a crude drug utilized for control purposes

Note 1 to entry: Marker substances contribute or not to the clinical efficacy. When they contribute to the clinical efficacy, however, evidence that they are solely responsible for the clinical efficacy can be available or not.

Note 2 to entry: Marker substances are generally employed when constituents of known therapeutic activity are not known or are not clearly identified, and are used to identify the crude drug or preparation or calculate their quantity in the finished product.

[SOURCE: WHO guidelines on good manufacturing practices (GMP) for herbal medicines, modified]

3.4
medicinal animal
animal (wild or bred) used for medicinal purposes

3.5
medicinal mineral
mineral used for medicinal purposes

3.6
medicinal plant
plant (wild or cultivated) used for medicinal purposes

Note 1 to entry: Medicinal plants include crude drugs which could be derived from lichen, algae, fungi or higher plants, such as leaves, flowers, fruit, fruiting bodies, seeds, stems, wood, bark, roots, rhizomes or other parts, which are entire, fragmented or powdered.

[SOURCE: WHO guidelines on good manufacturing practices (GMP) for herbal medicines, modified]

3.7
bulk product
product that has completed all processing stages up to, but not including, final packaging

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.8
crude drug
medicinal part obtained from plants or animals, cell inclusions and secretions separated from the origins, their extracts, and minerals

Note 1 to entry: Herbal materials include, in addition to medicinal parts, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs.

Note 2 to entry: In some countries, these materials are processed by various local procedures, such as steaming, roasting or stir-baking with honey, alcoholic beverages or other materials.

3.9
crude drug preparation
basis for finished traditional medicinal products that may include comminuted or cut crude drugs, or extracts, tinctures and fatty oils of crude drugs

Note 1 to entry: Crude drug preparations are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating crude drugs in alcoholic beverages and/or honey, or in other materials.

3.10
extract
preparation of liquid (liquid extracts and tinctures), semi-solid (soft extracts and oleoresins) or solid (dry extracts) consistency, obtained from medicinal plants, animals and minerals

3.11
finished product
finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling

Note 1 to entry: Natural products in this document includes finished products made from one or more crude drugs.

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.12
finished traditional Chinese medicinal product
product consisting of crude drug preparations made from one or more crude drugs

Note 1 to entry: If more than one crude drug is used, the term "mixture crude drugs product" can also be used.

Note 2 to entry: Finished traditional Chinese medicinal products and mixture crude drugs products contain excipients in addition to the active ingredients. However, finished traditional Chinese medicinal products or mixture crude drugs products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from crude drugs, are not considered to be crude drug products.

3.13
material of natural origin
medicinal plant, animal or mineral

3.14
pharmaceutical product
material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form

Note 1 to entry: It is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.15
starting material
substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.16
manufacture
operations of purchase of materials and products, production, quality control, release and storage of pharmaceutical products, and the related controls

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.17
manufacturer
company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.18
blending
process of combining materials or different batches to produce a homogeneous intermediate or finished product

[SOURCE: WHO guidelines on good manufacturing practices (GMP) for herbal medicines, modified]

3.19
packaging
operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product

Note 1 to entry: Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized would not normally be regarded as part of packaging.

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.20
production
operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.21
qualification
action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results

Note 1 to entry: The meaning of the word "validation" is sometimes extended to incorporate the concept of qualification.

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.22
quality assurance
concept covering all matters that individually or collectively influence the quality of a product

Note 1 to entry: It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

Note 2 to entry: Information on manufacturing control and quality control are provided in Annex A and B, respectively.

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.23
quarantine
physical or other effective means of isolation implemented while a decision is awaited on the release, rejection or reprocessing of starting or packaging materials, intermediates or bulk or finished products

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.24
specification
list of detailed requirements with which the products or materials used or obtained during manufacture have to conform

Note 1 to entry: They serve as a basis for quality evaluation.

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.25
validation
action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results

Note 1 to entry: See also *qualification* (3.21).

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.26
packaging material
material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment

Note 1 to entry: Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.27
contamination
undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.28
cross-contamination
contamination of a starting material, intermediate product or finished product with another starting material or product during production

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.29
clean area
area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.30
batch
lot
defined quantity of starting material, packaging material, or product that are processed in a single process or series of processes so that it is expected to be homogeneous

Note 1 to entry: It is sometimes necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Note 2 to entry: In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch corresponds to a defined fraction of the production, characterized by its intended homogeneity.

Note 3 to entry: The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

3.31
consignment
delivery
quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order

Note 1 to entry: A consignment comprises one or more packages or containers and includes material belonging to more than one batch.

[SOURCE: WHO good manufacturing practices for pharmaceutical products: main principles, modified]

4 Assurance of manufacturing process

4.1 Premises

4.1.1 General

As a general principle, premises shall be designed, located, constructed, adapted and maintained to suit the operations according to GMP, as the premises could be potentially affected by degradation and infestation of certain pests and are sensitive to microbiological contamination, production, and particularly storage of crude drugs and crude drug preparations.

4.1.2 Storage areas

a) Storage areas shall be well organized and tidy. Special attention shall be paid to cleanliness and good maintenance. Any accidental spillage shall be cleaned up immediately using methods that minimize the risk of cross-contamination of other materials, and shall be reported.

b) The areas shall be well labelled and crude drugs stored in such a way as to avoid any risk of cross-contamination. An area shall be identified for the quarantine of all incoming crude drugs.

NOTE 1 The set-up of storage areas depends on the type of crude drugs stored.

c) Storage areas shall be laid out to permit effective and orderly segregation of the various categories of materials stored, and to allow rotation of stock. Different crude drugs shall be stored in separate areas.

d) Duration of storage of any crude drugs in unpacked form shall be kept to a minimum.

NOTE 2 Minimum duration of storage protect stored material, and reduce the risk of pest attacks.

e) Incoming crude drugs shall be processed, unless specified otherwise, as soon as possible and shall be stored at appropriate temperature to prevent bacterial and fungal growth.

f) Where materials are stored in bulk, to reduce the risk of mould formation or fermentation it is advisable to store them in aerated rooms or containers using natural or mechanical aeration and ventilation. These areas shall also be equipped in such a way as to protect against the entry of insects or animals, especially rodents. Effective measures shall be taken to limit the spread of animals and microorganisms brought in with the crude drug and to prevent cross-contamination.

g) Crude drugs, even when stored in fibre drums, bags or boxes, shall be stored off the floor and suitably spaced to permit cleaning and inspection.

h) Appropriate steps shall be taken to ensure that conditions of humidity and temperature or protection from light are provided, maintained, monitored and recorded.

NOTE 3 The storage of crude drugs, extracts, tinctures and other preparations require special conditions of humidity and temperature or protection from light.

i) Crude drugs shall be kept in a dry area protected from moisture and processed following the principle of “first in, first out” (FIFO).

4.1.3 Production areas

a) Production areas shall comply with the general requirements of GMP.

b) As a rule, campaign work in their processing is necessary.

c) If feasible, the use of dedicated premises is encouraged.

d) The special nature of the production of traditional Chinese medicines requires that particular attention be given to processing products that generate dust.

e) When heating or boiling of the materials is necessary, a suitable air exhaust mechanism shall be employed to prevent accumulation of fumes and vapours.

f) Adequate precautions shall be taken during the sampling, weighing, mixing and processing of crude drugs, e.g. by use of dust extraction and air-handling systems to achieve the desired differential pressure and net airflow.

NOTE Adequate precautions facilitate cleaning and avoid cross-contamination.

4.1.4 Sanitation

a) A high-standard sanitation and hygiene requirement during manufacture is necessary.

NOTE 1 Crude drugs contain microbiological contaminants due to their natural origin. During harvesting and processing, traditional Chinese medicinal products could be contaminated by micro-organisms.

NOTE 2 High-standard sanitation and hygiene avoid alterations and reduce contamination.

b) The water supply to the manufacturing unit shall be monitored and, if necessary, treated appropriately to ensure consistency of quality.

c) The quality of water for manufacturing shall be drinking water grade or higher.

d) Waste from the manufacturing unit shall be disposed of regularly so as to maintain a high standard of hygiene in the manufacturing area.

e) Clearly marked waste-bins shall be available, emptied and cleaned as needed.

4.2 Documentation

4.2.1 General

The general principles for documentation shall comply with GMP.

The intended purpose for the specifications for crude drugs, crude drugs preparations and finished traditional Chinese medicinal products is to define the quality rather than establish full characterization and they shall focus on those characteristics found to be useful in order to ensure safety and efficacy.

Consistent quality for traditional Chinese medicines (finished traditional Chinese medicinal products) can only be assured if the starting crude drugs are defined in a rigorous and detailed manner. In some cases, more detailed information may be needed on aspects of collection or agricultural production.

For instance, the selection of seeds, conditions of cultivation and harvesting are important for reproducible quality of traditional Chinese medicines. Their characterization (which also includes a detailed evaluation of the botanical and phytochemical aspects of the crude drugs, manufacture of the crude drug preparation and the finished traditional Chinese medicinal product) is therefore essential to allow the establishment of specifications which are both comprehensive and relevant.

The specifications for crude drugs shall as far as possible include, as a minimum, information of crude drugs, finished traditional Chinese medicinal products, crude drug preparations, and processing instructions as described in the following clauses.

4.2.2 Crude drugs

a) The family and scientific name of the plant and animal shall be used according to the binomial system (genus, species, variety and the authority, i.e. the reference to the originator of the classification, e.g. *Linnaeus*).

b) The name of mineral shall be used according to the nomenclature of mineral standardized by the International Mineralogical Association (IMA).

c) Details of following items shall be included:

- the source of the plant and animal, such as country and/or region (also state and province, if applicable) of origin, whether it was cultivated or collected from the wild;
- where applicable, method of cultivation;
- dates and conditions of harvesting (e.g. whether there was extreme weather);
- collection procedures;
- collection area;
- brand, quantity and date of pesticide application, as required by the GACP of domestic and/or international regulations.

d) The following specifications for starting materials (and also of primary or printed packaging materials) shall be included, if applicable, reference to a pharmacopoeia monograph:

- whether the whole plant or only a part is used;

  NOTE 1 In the latter case, which part of the plant is used and its state, e.g. whole or reduced.

- for dried plant material, the drying system, if applicable;
- a description of the plant material based on visual (macroscopic) and/or microscopic examination;
- suitable identity tests including, where appropriate, identification tests (such as TLC or other chromatographic fingerprint) for known active ingredients or marker substances;

  NOTE 2 A reference sample is available for identification purposes.

- details of the assay, where appropriate, of active constituents or marker substances;
- result of limit tests such as dry residue of liquids, ash value (total ash, and ash insoluble in hydrochloric acid), water-soluble extractives, moisture/water content and loss on drying (taking into account the presence of essential oils if any);
- result of suitable methods for the determination of possible pesticide contamination and the acceptable limits for such contamination in crude drugs or crude drug preparations used in the manufacture of traditional Chinese medicines;
- result of tests for toxic metals and for likely contaminants, foreign materials and adulterants;
- result of tests for fungal and/or microbiological contamination, fumigant residues (if applicable), mycotoxins, pest-infestations, radioactivity and their acceptable limits;
- result of other appropriate tests (e.g. particle size, swelling index and residual solvents in crude drug preparations and biological fingerprints such as induced fluorescent marker substances).

4.2.3 Finished traditional Chinese medicinal products

a) The control tests and specifications for the finished traditional Chinese medicinal product shall be such as to allow the qualitative and quantitative determination of the main active constituents.

- If the therapeutic activity of constituents is known, these constituents shall be indicated in the documentation.
- If such substances are not known (e.g. because they are part of a complex mixture), the constituents useful for assessing the quality shall be identified as marker substances or fingerprints.

— In both cases, the assay (i.e. quantitative determination) specifications shall be defined.

— When the therapeutic activity of the constituents cannot be determined quantitatively, specifications shall be based on the determination of marker substances or fingerprints.

b) If either the final product or the crude drug preparation contains several crude drugs and a quantitative determination of each active ingredient is not feasible, the mixture of several active ingredients may be determined. The need for such a procedure shall be justified.

c) The concept of different acceptance criteria for release versus shelf-life specifications applies to finished traditional Chinese medicines only but not to crude drugs and crude drug preparations. Adequate retest periods shall be established for the latter. Examples where this may be applicable include assay and impurity (degradation product) levels:

— tests for microbiological contamination and tests for other toxicants;

— uniformity of weight (e.g. for tablets, single-dose powders, suppositories, capsules and herbal tea in sachets), disintegration time (for tablets, capsules, suppositories and pills), hardness and friability (for example, uncoated tablets), viscosity (for internal and external fluids), consistency (semisolid preparations), and dissolution (tablets or capsules), if applicable;

— physical appearance such as colour, odour, form, shape, size and texture;

— loss on drying, or water content;

— identity tests, qualitative determination of relevant substances of the crude drugs (e.g. fingerprint chromatograms);

— quantification of relevant active ingredients, if they have been identified, and the analytical methods that are available;

— limit tests for residual solvents.

4.2.4 Crude drug preparations

The specifications of crude drug preparations consist, depending on the preparation in question, of the relevant items of the specifications for crude drugs or for finished traditional Chinese medicinal products as outlined above.

4.2.5 Processing instructions

a) The processing instructions shall include the following items:

— descriptions of the different operations to be performed on the crude drug, such as drying, crushing, milling and sifting;

— the time and, if applicable, temperatures required in the drying process;

— the methods to be used to control fragment or particle size;

— instructions on removing foreign matter and other unwanted materials.

b) The drying conditions chosen shall be appropriate to the type of crude drug processed.

NOTE 1 The drying conditions depend on both the character of the active ingredients (e.g. essential oils) and the type of plant part collected (e.g. root, leaf or flower).

NOTE 2 Drying by direct exposure to sunlight, if not specifically contraindicated, is permitted, but drying on the ground is avoided.

NOTE 3 If the plant is processed fresh, without drying, the reasons and criteria determining the use of fresh material is stated.

c) For the production of processed extracts, the instructions shall specify details of any vehicle or solvent that may be used, the durations and temperatures needed for extraction, and any concentration stages and methods that may be required.

d) General instructions of manufacturing procedures to specify the manufacturing scale shall include the following items:

   a) input order of crude drugs;

   b) solvent ratio and solvents;

   c) rate of temperature increase;

   d) extraction temperature;

   e) extraction time;

   f) number of extraction;

   g) methods for solid-liquid separation;

   h) methods for concentration;

   i) methods for drying;

   j) details of other special methods, if applicable;

   k) yield and percentage yield in each manufacturing process;

   l) Drug extract ratio.

   NOTE 4 Standard ranges of yield and percentage yield are determined, taking into consideration crude drugs, manufacturing scale and other factors.

4.3 Personnel

4.3.1 General

General guidance in relation to personnel involved in the manufacture of medicinal products is given in the GMP of domestic and/or international regulations.

4.3.2 Crude drug control manager

4.3.2.1 General

Each manufacturing site dealing with crude drugs (whole, cut and powdered), bulk extracts, crude drugs as finished products and traditional Chinese medicinal products, shall assign qualified persons in charge of the management of crude drugs in a quality division.

4.3.2.2 Competence of crude drug control manager

The crude control manager shall have expertise in crude drugs and be able to discriminate and handle crude drugs and analysis.

4.3.2.3 Duties of crude drug control manager

a) The crude drug control manager shall have responsibility for the following and, if necessary, have the designated persons perform duties to control practically the matters concerning quality assurance of crude drugs:

   — raw materials for crude drugs;

— source of supply, etc. of crude drugs for traditional Chinese medicinal products;

— methods to collect samples from crude drugs;

— evaluation of authentication results (including morphological quality) among tests and examinations on crude drugs;

— education and training for persons in charge of handling crude drugs;

— other duties on quality assurance for crude drugs.

b) The release of traditional Chinese medicines shall be authorized by a person who has been trained in the specific features of the processing and quality control of crude drugs, crude drug preparations and finished traditional Chinese medicinal products.

c) Personnel dealing with the production and quality control of traditional Chinese medicines shall have adequate training in the specific issues relevant to traditional Chinese medicines and analysis.

4.3.3 Training

a) The personnel shall have adequate training in appropriate fields such as pharmaceutical technology, taxonomic botany, phytochemistry, pharmacognosy, hygiene, microbiology and related subjects (such as traditional use of crude drugs).

b) Training records shall be maintained and periodic assessments of the effectiveness of training programmes shall be made.

4.3.4 Personnel hygiene

a) Personnel entrusted with the handling of crude drugs, crude drugs preparations and finished traditional Chinese medicinal products shall be required to have a high degree of personal hygiene and to have received adequate training in maintaining appropriate standards of hygiene.

b) The personnel shall not be on duty if they have infectious diseases or skin diseases.

c) Written procedures listing the basic hygiene requirements shall be made available.

d) Personnel shall be protected from contact with toxic irritants and potentially allergenic plant materials by means of adequate protective clothing.

4.4 Change control

a) In cases where any change will be made in the manufacturing procedure, etc. which could affect the quality of the products, the manufacturer shall designate beforehand a person to conduct the following duties in accordance with the documented procedure:

— to evaluate the effects on the quality of the products due to such change;

— to obtain approval from the manufacturing manager with respect to the change being made based on the results of the evaluation;

— to establish and maintain records of the evaluation and approval.

b) The manufacturer shall revise relevant documents, train the personnel and take other necessary actions in cases where any change is made upon approval of the manufacturing manager.

4.5 Deviation control

a) In case any deviation from the manufacturing procedure, etc. has occurred, the manufacturer shall direct the person designated beforehand to evaluate effects on the quality of the products due to the deviation.

b) The manufacturing manager shall permit the designated person to take proper actions based on the results of the evaluation.

c) The manufacturer shall direct the designated person to establish and to maintain records of the evaluation in a CAPA (corrective action/preventive action) process.

d) The manufacturer shall revise relevant documents, train personnel and take other necessary actions.

4.6 Self-inspections

The manufacturer, etc. shall have the person designated beforehand to conduct the following duties:

— to conduct the self-inspections periodically on the manufacturing control (manufacturing control shall be in accordance with Annex A) and quality control (quality control shall be in accordance with Annex B) of the products in their manufacturing site, and to establish and maintain records of it;

— to report in writing the results of the self-inspections to the manufacturing manager;

— to take necessary action in cases where improvements are necessary, and to establish and maintain records of such actions.

Annex A
(normative)

Manufacturing control

A.1 General

To ensure not only the quality, but also the safety and efficacy of complex products of natural product origin such as traditional Chinese medicines, it is essential that the steps in their production are clearly defined.

Collection/cultivation and/or harvesting of medicinal plants shall follow other relevant guidance such as GACP of domestic and/or international regulations.

Generally, postharvest processing including primary cutting is (or shall be) covered by GACP. If further comminuting is carried out in the manufacturing processing, it shall be covered by GMP, or by these supplementary guidelines. If cutting and comminuting considerably reduce the probability of detection of adulteration or mix-up of crude drugs, application of these supplementary guidelines may be extended to encompass these steps.

The manufacturing process shall be controlled particularly in relation to the prevention of contamination by microorganisms, based on the fact that crude drugs and bulk extracts have nutrient-rich environments for microorganisms.

A.2 General considerations

Materials shall be handled in a fashion that is not detrimental to the product. On arrival at the processing facility, the crude drug shall be promptly unloaded and unpacked. During this operation, the crude drug shall not come into direct contact with the soil. Moreover, it shall not be exposed directly to the sun (except in cases where this is a specific requirement, e.g. sun-drying) and it shall be protected from rain and microbiological contamination.

Attention shall be paid to "classification" of clean area requirements taking into account the possible high degree of initial microbial contamination of crude drugs. Classification of premises as applied to sites for the production of other pharmaceutical substances may not be applicable to processing of crude drugs. Specific and detailed requirements shall be developed to cover microbial contamination of equipment, air, surfaces and personnel, and also for rest rooms, utilities, ancillary and supporting systems (e.g. water and compressed air).

Care shall be taken to choose cleaning methods appropriate to the characteristics of the crude drugs being processed. Washing dried crude drugs with water is generally inappropriate. When it is necessary to clean them, an air duster or air shower shall be employed. In cases when immersion of crude drugs in water or other appropriate agents (such as disinfectants) for cleaning is unavoidable (e.g. to eliminate suspected coliform bacteria), it shall be kept to a minimum and documented.

The presence of plant materials from different species and varieties, or different plant parts shall be controlled during the entire production process to avoid contamination, unless it is assured that these materials are equivalent.

A.3 Mixing of batches and blending

Crude drugs with constituents of known therapeutic activity are often standardized (i.e. adjusted to a defined content of such constituents). The methods used to achieve such standardization shall be

documented. Blending different batches of a specific crude drug (e.g. before extraction) or by mixing different lots of similar crude drug preparations may also be acceptable. Records shall be maintained to ensure traceability. The blending process shall be adequately controlled and documented and the blended batch shall be tested for conformity with established specifications where appropriate.

Batches shall be mixed only if it can be guaranteed that the mixture will be homogeneous. Such processes shall be well documented.

Out-of-specification batches of crude drugs shall not be blended with other batches for the purpose of meeting specifications, except for standardization of the content of constituents with known pharmaceutical therapeutic effects. Every batch incorporated into the blend shall have been manufactured using an established process and shall have been individually tested and found to meet appropriate specifications prior to blending.

Where particular physical attributes of the material are critical, blending operations shall be validated to show uniformity of the combined batch. Validation shall include testing of critical attributes (e.g. particle size distribution, bulk density and tap density) that may be affected by the blending process.

The expiry date of the blended batch shall be chosen according to the date of manufacture of the oldest batch in the blend.