Hong Kong
Good Manufacturing Practice Guidelines for Proprietary Chinese Medicines

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Contents

Introduction		1
Glossary		2
Chapter 1	Quality Management in the Chinese Medicines Manufacturing Industry	7
Chapter 2	Personnel	12
Chapter 3	Premises	17
Chapter 4	Equipment	23
Chapter 5	Documentation	25
Chapter 6	Manufacture	34
Chapter 7	Validation	44
Chapter 8	Quality Control	45
Chapter 9	Contract Manufacture and Test	52
Chapter 10	Complaints	55
Chapter 11	Product Recalls	57
Chapter 12	Self-Inspection and Quality Audits	59
Appendix	Sterile Proprietary Chinese Medicines	62

Introduction

The guidelines have been prepared by the Chinese Medicines Board under the Chinese Medicine Council of Hong Kong for the purpose of promoting the standardization of the proprietary Chinese medicines manufacturing industry. The Council wishes to assure the quality and safety of proprietary Chinese medicines and thus, to safeguard public health and to boost the public confidence in using proprietary Chinese medicines.

These standards and generals of the guidelines can serve as references for the personnel engaged in the Chinese medicines manufacturing industry, so that they can follow the requirements of good practices in manufacture and quality control of proprietary Chinese medicines.

The guidelines cover more than the fundamental items of Good Manufacturing Practice in respect of proprietary Chinese medicines, but also include the matters requiring attention in the manufacture of sterile proprietary Chinese medicines supplemented in the appendix.

The guidelines do not restrain the development of new concepts and new technologies. Manufacturer can still, through appropriate validation, adopt any new concepts and new technologies provided that the quality assurance is equivalent to the generals set out in the guidelines.

Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other documents.

Active ingredient
A substance or compound used or intended to be used in the manufacture of a proprietary Chinese medicine and that contributes to the pharmacological effect or effects of proprietary Chinese medicine (e.g. herbal medicine, processed herbal medicine, extract of herbal medicine or extract of processed herbal medicine).

Airlock
An isolated space with two or more doors, which is interposed between two or more rooms of differing grades of air cleanliness, for the purpose of controlling the air flow between those rooms when they need to be entered. An airlock is used by either personnel or materials.

Authorized person
The person responsible for the release of every batch of finished products for sale.

Batch
A defined quantity of starting material, packing material or product produced in a single process or series of processes so that it could be expected to be homogeneous. In the case of continuous production, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Batch number
A series of numbers, letters or other symbols, or a series consisting of a combination of numbers, letters and other symbols, used for the purpose of identifying when or by whom the proprietary Chinese medicine is produced.

Batch numbering system
Standard operating procedure (SOP) describing the details of the batch numbering.

Batch records

These include all documents associated with the production of a batch of product or manufacture of a batch of finished product. Batch records provide a history of manufacture and all circumstances pertinent to the quality of each batch of product or finished product.

Bulk product

Any product that has completed all production processes up to, but not including, final packing of finished product.

Calibration

The set of operations which establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Clean area

An area with environmental control of particulate and microbiological contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

Critical manufacturing process

A manufacturing process which may cause variation in the quality of the product.

Critical packing process

A packing process which may cause variation in the quality of the product.

Critical production process

A production process which may cause variation in the quality of the product.

Cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or product during the course of manufacture.

Finished product

A product that has undergone all manufacturing processes, including packing in its final container and labelling.

In-process control

Control measures taken during manufacture in order to, if necessary, adjust the manufacturing process to ensure that the product complies with the requirements of its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate product

Partly processed material which must undergo further production processes before it becomes a bulk product.

Large volume parenterals

Sterile solutions intended for parenteral application with a volume of 100 ml or more.

Manufacture and Manufacturer

Manufacture means the preparation, production, packing or re-packing of the proprietary Chinese medicine for sale or distribution, and manufacturer shall be construed accordingly.

Master formula

A document or set of documents specifying the starting materials with their quantities and the packing materials, together with a description of the processes and precautions required to manufacture a specified quantity of a finished product as well as the production instructions (including the in-process controls).

Master record

Documents that serve as a basis for the batch documentation (blank batch record).

Packing material

Any material, including printed packing material, employed in the packing of a proprietary Chinese medicine, excluding any outer package used for transportation or shipment. Packing materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Packing process

All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. Sterile filling would not normally be regarded as part of the packing process, the bulk product being the filled, but not the finally packed, primary container.

Processed herbal medicine

The processed form of a herbal medicine which has passed through treatment like cleaning, cutting, roasting or broiling, so as to comply with the requirements of its specifications and is thus suitable for the manufacture of proprietary Chinese medicines.

Proprietary Chinese medicine

Proprietary Chinese medicine means any proprietary product –

(a) composed solely of the following as active ingredients -
    (i) any Chinese herbal medicines; or
    (ii) any materials of herbal, animal or mineral origin customarily used by the Chinese; or
    (iii) any medicines and materials referred to in subparagraphs (i) and (ii) respectively;
(b) formulated in a finished dose form; and
(c) known or claimed to be used for the diagnosis, treatment, prevention or alleviation of any disease or any symptom of a disease in human beings, or for the regulation of the functional states of the human body.

Quality control

Concerned with sampling, making specifications and testing, and with the organized system, documentation and release procedures, which ensure that the necessary and relevant tests are actually carried out and that only materials and products with satisfactory quality are released for use, and for sale or supply respectively.

Quarantine

The status of starting or packing materials, intermediate products, bulk products or finished products stored in a defined area, or by other effective means of isolation, while a decision is awaited on their release, rejection or reprocessing.

Reconciliation

A comparison, making due allowance for normal variation, between the amount of product or materials theoretically produced or used and the amount actually produced or used.

Recovery (or Blending)

The introduction of all, or part, of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined manufacturing process.

Reprocessing
The reworking of all, or part, of a batch of product of an unacceptable quality from a defined manufacturing process so that its quality may be rendered acceptable by one or more additional operations.

Returned product
Finished product sent back to the manufacturer.

Specifications
A document describing in detail the requirements with which the products or materials used or obtained during the course of manufacture have to conform. It serves as a basis for quality evaluation.

Standard operating procedure (SOP)
An approved written procedure giving instructions for performing operations not necessarily specific to a given product or material, but of a more general nature (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and checking). Certain standard operating procedures may be used to supplement product-specific master formula, master record or batch documentation.

Starting material
Any substance, that complies with the requirements of its specification, used in the manufacturing processes of a proprietary Chinese medicine, but excluding packing materials.

System
A regulated pattern of interacting activities and techniques that are united to form an organized whole.

Validation
The documented act of proving that any procedure, manufacturing process, equipment, material, activity or system actually leads to the expected results.

Chapter 1 Quality Management in the Chinese Medicines Manufacturing Industry

Principle

The manufacturer must assume responsibility for the quality of the proprietary Chinese medicines to ensure that they are fit for their intended use and comply with the requirements of the Chinese Medicine Ordinance. Proprietary Chinese medicines must be safe and must have appropriate level of quality and efficacy and must not adversely affect the health of the users. The attainment of this quality objective is the responsibility of senior management. To achieve the quality objective, there must be participation and commitment of staff in different departments and at all levels within the organization, the suppliers and the distributors, and a comprehensively designed and correctly implemented system of quality assurance incorporating good manufacturing practice (GMP) and quality control. The quality assurance system should be fully documented and its effectiveness monitored. All segments of the quality assurance system should be appropriately staffed with competent personnel and should have suitable premises and suitable and sufficient equipment and facilities.

Quality management is defined as the aspect of management function that determines and implements the "quality policy" as formally expressed and authorized by top management. "Quality policy" is the overall intention and direction of an organization regarding quality.

The basic elements of quality management are as follows:

a. an appropriate infrastructure encompassing the organizational structure, procedures, processes and resources; and
b. systematic measures taken to ensure that a product will satisfy defined quality requirements. All such measures are referred to as "quality assurance".

1.1 The concepts of quality assurance, GMP and quality control are interrelated aspects of quality management. They are described here in order to emphasize their relationship and their fundamental importance to the manufacture and control of proprietary Chinese medicines.

Quality Assurance

1.2 "Quality assurance" is a wide-ranging concept covering all measures which individually or collectively influence the quality of a product. Quality assurance consists of all the arrangements made with a view to ensuring that proprietary Chinese medicines are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of these guidelines such as product design and development.

In the manufacture of proprietary Chinese medicines, a quality assurance system should ensure that:

a. proprietary Chinese medicines are designed and developed in a way that the requirements of GMP and other associated codes, such as good laboratory practice (GLP) for medicines, good clinical practice (GCP) for medicines and good agricultural practice (GAP) for Chinese herbal medicines, are considered;
b. manufacturing processes and quality control measures are clearly specified in a written form and those contents should comply with GMP requirements;
c. managerial responsibilities are clearly specified in duty descriptions;
d. measures are made for the production, supply and use of the correct starting materials and packing materials;
e. all necessary controls on starting materials, intermediate products, bulk products and other in-process controls, calibrations and validations are carried out;
f. the finished product is correctly manufactured and checked, according to the defined procedures;
g. proprietary Chinese medicines are not sold or supplied until the authorized person (please refer to section 2.4) certifies that each batch of product has complied with the requirements of the Chinese Medicine Ordinance in respect of their manufacture, control and release;
h. appropriate measures are made for the manufacturer to store and distribute proprietary Chinese medicines in a suitable manner and to provide appropriate after-sale service of proprietary Chinese medicines; and
i. there is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system.

Good Manufacturing Practice in respect of proprietary Chinese medicines

1.3 "Good Manufacturing Practice" is that part of quality assurance aimed at ensuring that proprietary Chinese medicines are consistently manufactured, and controlled to the requirements of appropriate specifications with respect to their intended use. The objective of implementing GMP is mainly to diminish the risks inherent in any proprietary Chinese medicine manufacturing processes that cannot be completely avoided through the test of final products. Such risks are essentially of two types: cross-contamination (in particular by unexpected contaminants) and mix-ups caused by false labels being put on containers.

While implementing GMP:

a. all manufacturing processes should be clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing products that comply with the requirements of their specifications;
b. critical manufacturing processes, and any significant changes made to the processes, must be validated;
c. all necessary facilities are provided, including:
    (i.) appropriately qualified and trained personnel;
    (ii.) suitable premises and adequate space;
    (iii.) suitable equipment and services;
    (iv.) correct materials, containers and labels;
    (v.) approved procedures and instructions;
    (vi.) suitable storage and transport; and
    (vii.) adequate personnel, laboratories and equipment, or in-process controls under the responsibility of the manufacturing department;
d. instructions and procedures must be written in clear and unambiguous language, and should be specifically applicable to the facilities provided;
e. operators should be trained to carry out procedures correctly;
f. records must be made, manually and/or by recording instruments, during manufacture to show that all the steps required by the procedures and instructions have in fact been taken and that the yield and quality of the product are as expected, and that any significant deviations must be fully recorded and investigated;
g. records covering manufacture and sales of products that enable the complete history of manufacture and distribution of a batch to be traced, are retained in a comprehensive and accessible form;

h. the products should be properly stored and distributed to minimize any risk to their quality;
i. a system is set up to recall any batch of product to avoid such from sale or supply; and
j. complaints about marketed products are examined, the causes of quality defects are investigated, and appropriate measures are taken in respect of any defective products and to avoid recurrence.

Quality Control

1.4 "Quality control" is that part of GMP concerned with sampling, making specifications and testing, and with the organized system, documentation and release procedures, which ensure that the necessary and relevant tests are actually carried out and that only materials and products with satisfactory quality are released for use, and for sale or supply respectively. Quality control is not confined to laboratory operations. It must include all decisions concerning the quality of the product.

The basic requirements of quality control are as follows:

a. adequate facilities, trained personnel and approved procedures must be available for sampling, checking and testing of starting materials, packing materials, intermediate products, bulk products and finished products, and where appropriate, for monitoring environmental conditions for GMP purposes;
b. samples of starting materials, packing materials, intermediate products, bulk products and finished products must be taken in accordance with the approved methods, by personnel nominated by the quality control department;
c. test methods must be validated;
d. records must be made, manually and/or by recording instruments, to demonstrate that all the required sampling, checking and test procedures have actually been carried out and that any deviations must be fully recorded and investigated;
e. ingredients of finished product must comply with the specified quality requirements of the product; the ingredients must be stored in suitable containers with correct labels;

f. materials, intermediate products, bulk products and finished products must be checked and tested against the requirements of their specifications, and the results must be recorded. Product assessment must include a review and evaluation of the relevant manufacturing documentation and an assessment of deviations from specified procedures;
g. an authorized person should ensure that each batch of product complies with the requirements of the Chinese Medicine Ordinance, and so certify the products released for sale or supply; and
h. sufficient samples of starting materials and products must be retained for future testing, whenever that may be necessary. The product sample should be retained in its final pack, unless the pack is exceptionally large.

Chapter 2 Personnel

Principle

People are the deciding factor in the establishment and maintenance of a satisfactory system of quality assurance and in the correct manufacture and control of proprietary Chinese medicines. Therefore, there must be sufficient qualified personnel to carry out relevant duties. All personnel should understand their responsibilities clearly and such responsibilities should be documented. Moreover, all personnel should be aware of the principles of GMP that are relevant to them.

General

2.1 The manufacturer should have an adequate number of competent personnel with practical experience. The management responsible for the manufacture and quality control of proprietary Chinese medicines must possess professional knowledge of Chinese medicines. The responsibilities placed on any one individual should not be so extensive as to affect the quality of product.

2.2 The manufacturer should have an organization chart. All levels of management should have their written duty descriptions and adequate authority to carry out their duties. Their duties may be delegated to designated deputies who have appropriate qualifications. There should be no gaps, or unnecessary overlaps, in the responsibilities of personnel concerned with the application of GMP.

2.3 All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene education, according to their needs. Personnel should be motivated to actively establish and maintain high-quality standards, by manufacturer.

Key Personnel

2.4 Key personnel includes the head of manufacturing department, the head of quality control department, the head of sales/distribution department and the authorized person. In general, key posts should be occupied by full-time personnel. The heads of manufacturing and quality control departments should be independent of each other. It may be necessary to delegate some of the tasks to deputies, however, the responsibility should not be delegated.

2.5 The heads of the manufacturing and quality control departments should have adequate relevant qualifications and practical experience. In order to gain such experience, newly joined department heads should exercise their duties with the advice of staff with such practical experience. The heads of the manufacturing and quality control departments should be able to exercise independent judgement based on the application of scientific principles and the understanding of the practical problems encountered in the manufacture and quality control of proprietary Chinese medicines.

2.6 The head of the manufacturing department has the following responsibilities:

a. to ensure that products are manufactured and stored according to the appropriate standard operating procedures to achieve the required quality;
b. to approve the production instructions and packing instructions, including in-process controls, and to ensure their strict implementation;
c. to ensure that the manufacturing records are evaluated and signed by a designated person before they are made available to the quality control department;
d. to check the appropriate maintenance of the manufacturing department, premises and equipment;
e. to ensure that the manufacturing processes are validated and control instruments are calibrated and the relevant results are recorded in reports; and
f. to ensure that the initial and continuing training of manufacturing personnel is carried out and adapted according to need.

2.7 The head of the quality control department has the following responsibilities:

a. to approve or reject starting materials, packing materials, intermediate products, bulk products and finished products;
b. to evaluate batch records;
c. to ensure that all necessary tests are carried out;
d. to approve sampling instructions, specifications, test methods and other quality control procedures for materials, intermediate products, bulk products and finished products;
e. to approve and monitor any test carried out under contract;
f. to check the appropriate maintenance of the quality control department, premises and equipment;
g. to ensure that the test methods are validated and quality control equipment are calibrated; and

h. to ensure that the initial and continuing training of quality control personnel is carried out and adapted according to need.

Other responsibilities of the quality control department are summarized in Chapter 8 “Quality Control”.

2.8 The heads of the manufacturing and quality control departments have the following shared responsibilities relating to product quality:

a. the approval and revision of standard operating procedures and documents;
b. the monitoring and control of the manufacturing environment;
c. the maintenance of the hygiene of premises;
d. the validation of the processes and calibration of test equipment;
e. the provision of training to personnel;
f. the approval and monitoring of suppliers of materials;
g. the approval and monitoring of contract manufacturers;
h. the designation and monitoring of storage conditions for materials and products;
i. the retention of records;
j. the monitoring of implementation of GMP; and
k. through the checking, investigation and sampling, to monitor factors that may affect product quality.

Training

2.9 The manufacturer should provide training in accordance with a written programme for all personnel who work in the manufacturing areas or the quality control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel who could affect the quality of the product.

2.10 Besides training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to their duties. Moreover, continuing training should also be provided and its practical effectiveness should be assessed periodically, by manufacturer. Training programmes should be prepared by the head of either the manufacturing or the quality control department. Training records should be kept.

2.11 Personnel responsible for checking herbal medicines or processed herbal medicines upon receipt should be given relevant training to enrich their knowledge of identification and quality assessment of herbal medicines or processed herbal medicines.

2.12 Personnel responsible for handling highly active, toxic, infectious or sensitizing materials should be given specific training.

2.13 Visitors or untrained personnel should not enter the manufacturing and quality control areas. If this is unavoidable, they should be reminded of the matters needing special attention, such as personal hygiene and the method of wearing protective clothing. They should be closely supervised.

2.14 The concept of quality assurance and all the topics capable of improving its understanding and implementation should be fully discussed during the training sessions.

Personal Hygiene

2.15 The manufacturer should devise personal hygiene measures including health checks, maintaining personal hygiene and setting requirements of working clothing.

2.16 All personnel, prior to and during employment, should undergo health checks. Personnel conducting visual on-line checking should also undergo periodic eye checks.

2.17 Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packing materials, intermediate products, bulk products or finished products until the condition is no longer judged to be a risk.

2.18 Personal hygiene procedures, including the wear of appropriate clean working clothing, should apply to all persons entering the manufacturing areas.

2.19 In order to protect the product against contamination, personnel should wear clean working clothing, foot coverings and hair covering appropriate to the duties they perform. The working clothing should be smooth, non-static and shed no fibres and particles. The use of working clothing should be appropriate to the manufacturing environment. Used clothes, if reusable, should be stored in closed containers for washing. The manufacturer should devise cleaning and sterilization procedures for working clothing. The clothing should be laundered and, if necessary, sterilized according to relevant requirements.

2.20 Smoking, eating, drinking, chewing, and keeping of materials irrelevant to the manufacturing processes, such as plants, food, drink, smoking materials and personal medicines, are not permitted in the manufacturing, quality control and storage areas or in any other areas where they might adversely affect product quality.

2.21 All personnel should be trained of personal hygiene. A high level of personal hygiene should be observed by all personnel. Personnel should be instructed to wash their hands before entering manufacturing areas. Signs to this effect should be posted to remind personnel to observe the instructions.

2.22 Direct contact should be avoided between the hands of personnel and starting materials, primary packing materials, intermediate products or bulk products.

2.23 All personnel should be instructed and encouraged to report to their immediate supervisor any conditions that may be considered to adversely affect the product quality, including the factors of premises, equipment or personnel.

Chapter 3 Premises

Principle

Premises must be located, designed, constructed, adapted and maintained to suit the manufacturing processes to be carried out. Their layout and design must aim to minimize the risk of errors and to permit effective cleaning and maintenance in order to avoid cross-contamination, accumulation of dust or dirt, and any adverse effect on the quality of products.

General

3.1 The situation of premises should, when considered together with measures to protect the manufacturing process, prevent materials and products from being contaminated.

3.2 Premises should be designed and constructed to facilitate good sanitation.

3.3 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products. Premises should be cleaned and, where applicable, disinfected according to procedures.

3.4 Appropriate facilities for electrical supply, lighting, ventilation, temperature and humidity regulator should be available and such that they do not adversely affect, directly or indirectly, either the quality of the products during their manufacture and storage, or the accurate functioning of equipment. Emergency lighting should be available.

3.5 Premises should be designed and equipped so as to protect against entry of insects or other animals.

3.6 Appropriate measures should be taken to prevent personnel without approval from entering the manufacturing, storage and quality control areas. Personnel who do not work in these areas should not make use of such areas as a passageway.

Manufacturing Areas

3.7 The areas for manufacturing proprietary Chinese medicines, and other medicinal products, should be separated and equipped with dedicated manufacturing equipment and air purifying system. If this cannot be done, effective protective measures should be taken and the necessary validations should be conducted to prevent cross-contamination. Highly toxic chemicals, such as pesticides and herbicides, should not be manufactured in the premises.

3.8 Pre-treatment of herbal medicines, extraction and concentration of processed herbal medicines and washing or processing of animal organs and tissues, must be separated from the manufacture of proprietary Chinese medicines.

3.9 Premises should preferably be laid out in such a way as to allow the manufacture to take place in areas connected in a logical order corresponding to the sequence of the manufacturing processes and to allow the environment of manufacturing areas to achieve the requisite air cleanliness.

3.10 The manufacturing areas should be of adequate space, having regard to the scale of the operation and the positioning of equipment and materials, to minimize the risk of mix-ups of different products and materials, to avoid cross-contamination and to minimize the risk of errors in manufacture.

3.11 The areas for processing herbal medicines, such as steaming, stir-baking, broiling or calcining, should be of adequate space, having regard to the scale of the operation and the positioning of equipment and materials, to minimize the risk of mix-ups, to avoid cross-contamination and to minimize the risk of errors in processing.

3.12 The areas for extraction and concentration of processed herbal medicines should be of adequate space, having regard to the scale of the operation and the positioning of equipment and materials, to minimize the risk of mix-ups, to avoid cross-contamination and to minimize the risk of errors in manufacture.

3.13 A bench for screening herbal medicines or processed herbal medicines should be available. The surface of the bench should be smooth and it should not shed particulate matter.

3.14 Where starting materials, primary packing materials, intermediate products and bulk products are exposed in the manufacturing areas, the interior surfaces of the areas should be smooth and free from cracks and open joints. They should not shed particulate matter, and should permit easy cleaning. When necessary, the areas should be disinfected.

3.15 Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

3.16 Drains should be of adequate size and equipped to prevent back-flow. Open channels should be avoided where possible. If drains are necessary, they should be shallow to facilitate cleaning and disinfection.

3.17 Manufacturing areas should be equipped with air control facilities (including control of temperature and, where necessary, control of humidity and air filtration) appropriate to the products manufactured, the manufacturing processes undertaken and the external environment. The environment of these manufacturing areas should be regularly monitored during manufacture and non-manufacture periods, to ensure compliance with the design specifications.

3.18 The areas for processing herbal medicines, such as steaming, stir-baking, broiling or calcining, should be equipped with facilities for good ventilation, and the control of smoke, dust and temperature. The areas for sifting, cutting and milling of herbal medicines should be equipped with facilities for effective dust control and air exhaustion.

3.19 The areas for extraction and concentration of processed herbal medicines should be equipped with facilities for good air exhaustion and prevention of contamination and cross-contamination. The collection point of extract and concentrate should be equipped with a device supplying air of appropriate quality.

3.20 The weighing of starting materials and products should usually be carried out in separate weighing areas designed for that purpose, with facilities for controlling dust.

3.21 Areas for packing proprietary Chinese medicines should be suitably designed and laid out to prevent mix-ups or cross-contamination.

3.22 Manufacturing areas should be well lit, particularly where visual on-line checking is carried out.

3.23 In-process control may only be carried out in manufacturing areas provided that there is no adverse effect on the quality of products.

Storage Areas

3.24 Storage areas should be of sufficient capacity to allow orderly storage of the starting materials, packing materials, intermediate products, bulk products, products in quarantine, released products, rejected products, returned products and recalled products. Solids and liquids should be stored separately. The storage of volatile materials should avoid causing any contamination to other materials. Processed, sorted or treated herbal medicines should be stored in clean containers or packages and stored separately from untreated or unprocessed herbal medicines. Toxic or very expensive herbal medicines should be stored in cabinets or areas specifically designed for such use.

3.25 Storage areas should be designed and equipped to ensure good storage conditions. They should be clean, dry and maintained within suitable limits of temperature. Where special conditions of temperature and humidity for storage of the materials and products are required, these should be provided, monitored and controlled. The storage of herbal medicines and processed herbal medicines should facilitate proper maintenance of the medicines.

3.26 Receive and dispatch of products and materials should not be conducted in exposed areas. Containers of materials should be cleaned, if necessary, before storage.

3.27 Separated areas for storing materials and products in quarantine should be set up and clearly marked. Personnel without approval should not have access to these areas. Any system replacing the physical quarantine should provide an equivalent level of security.

3.28 There should be a dedicated sampling room for starting materials. If there is no such room for sampling, sampling should be conducted in such a way as to prevent contamination or cross-contamination.

3.29 Segregation should be provided for the storage of rejected, recalled or returned materials or products.

3.30 All toxic or inflammable materials or products should be stored in safe and segregated areas.

3.31 Printed packing materials should be stored in safe and segregated areas according to their categories.

Quality Control Area

3.32 Quality control laboratories should be separated from manufacturing areas. Laboratories where biological, microbiological or radioisotope tests are employed should be separated from each other.

3.33 The design and space of quality control laboratories should correspond to the tests carried out, to avoid mix-ups and cross-contamination. There should be adequate and suitable space for storing samples, Chinese medicine specimens, reference standards and records. Appropriate storage conditions should be provided, where necessary.

3.34 The quality control laboratories should be constructed with suitable materials and equipped with fumes prevention and ventilation facilities. A separate air purifying system, and relevant equipment should be available in biological, microbiological and radioisotope laboratories.

3.35 Instruments with special requirements should be stored in specified rooms with appropriate facilities, to guard against any electrical interference, vibration, contact with excessive moisture or other external factors.

Ancillary Areas

3.36 Staff rest and refreshment rooms should be separated from other areas.

3.37 Facilities for changing and storing clothes and for washing and toilet purposes should be provided according to the number of users. Toilets should be separated from manufacturing and storage areas.

3.38 Maintenance workshops should be separated from manufacturing areas, as far as possible. Whenever parts and tools are stored in the manufacturing areas, they should be kept in rooms or lockers specifically designed for that use.

3.39 Animal houses should be strictly separated from other areas, with separate entrances for animals and with separate air purifying system.

Chapter 4 Equipment

Principle

Equipment must be located, designed, constructed, adapted and maintained to comply with the requirements of the manufacturing processes of proprietary Chinese medicines to be carried out. The layout and design of equipment should aim to minimize the risk of errors and to permit effective cleaning and maintenance in order to avoid cross-contamination, accumulation of dust or dirt, and any other factors that may adversely affect the quality of products.

General

4.1 Manufacturing equipment should be designed, located and maintained to serve its intended purposes.

4.2 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned regularly.

4.3 Suitable washing and cleaning equipment should be chosen. The equipment and their methods of usage should not be sources of contamination.

4.4 Equipment should be installed in such a way as to minimize any risk of error, or of contamination.

4.5 Repair and maintenance operations of equipment should not present any hazard to the quality of products.

4.6 Manufacturing equipment should not present any hazard to the quality of products. The surface of the manufacturing equipment that contacts directly the starting materials, intermediate products, bulk products or finished products should be made from materials that are not reactive, additive and absorptive, to avoid affecting the quality of products. Lubricants, coolants, etc. for manufacturing equipment should not cause any contamination to the products or containers.

4.7 Quality control equipment and instruments should be suitable for the test methods undertaken.

4.8 Balances and other measuring equipment used for manufacturing and quality control of products should be of an appropriate range and precision to meet the requirements of the manufacturing processes and quality control. They should be calibrated regularly.

4.9 Measuring, weighing, recording and control equipment and instruments should be serviced and calibrated regularly and records should be maintained accordingly. The functions of test instruments should be checked daily or prior to use.

4.10 The date of calibration and servicing and the date when re-calibration is due should be clearly indicated on the equipment.

4.11 Measuring, weighing, recording and control equipment should be calibrated and checked regularly by appropriate methods. Records should be kept accordingly.

4.12 Pipework should be designed and installed to avoid dead legs. All piping should be non-toxic and resistant to corrosion. Fixed pipework should be clearly labelled with the contents and the direction of flow.

4.13 Piping for water used in the manufacturing process should be sanitized according to procedures that detail the action limits for microbiological contamination and the corrective measures to be taken as necessary.

4.14 Measures should be made to indicate failures of equipment or services (e.g. water or gas supply facilities). Defective equipment should be withdrawn from use until the defect has been rectified. Manufacturing equipment should be cleaned according to procedures and stored under clean and dry conditions.

4.15 Defective equipment should be removed from manufacturing and quality control areas as far as possible, or at least be clearly labelled as defective.

Chapter 5 Documentation

Principle

Documentation is a fundamental part of the quality assurance system and, as such, should be related to all aspects of the requirements of GMP. The provision of a good documentation system is aimed to define the specifications for all materials and products, and methods of manufacture and quality control, to ensure that all personnel concerned with manufacture know what to do and when to do it, to ensure that the authorized person has all the information necessary to decide whether or not to release a batch of products for sale, and to provide information that will permit investigation of the history of any suspected defective batch. The manufacturer can design formats of documents and decide the use of such documents. In some circumstances, some or all of the documents described below may be brought together, but they will usually be separate.

General

5.1 Documents should be designed, prepared, reviewed and distributed with care.

5.2 Documents should be approved, signed and dated by the relevant responsible personnel. No document should be changed without approval.

5.3 Documents should have unambiguous contents and should be laid out in an orderly fashion and be easy to read. The title, nature and purpose should be clearly stated on documents. For each category of document, there should be a coding system and a date, to differentiate these documents and their nature. Reproduced documents should be clear and legible. The reproduction of working documents from master documents should assure that no error would be introduced during the reproduction process.

5.4 Documents should be regularly reviewed and revised. After a document has been revised, inadvertent use of the superseded documents should be prevented.

5.5 Where documents require the entry of data, sufficient space should be provided and these entries should be clear, legible and indelible.

5.6 Any alteration made to a document should be signed and dated by the relevant responsible personnel. The alteration should permit the reading of the original information. When necessary, the reason for the alteration should be stated.

5.7 Any action taken during the course of manufacture should be recorded, so that all significant activities concerning the manufacture of product can be traced. Relevant records and standard operating procedures should be retained for at least two years after the expiry date of the products.

5.8 Data may be recorded by electronic data processing systems or by photographic or other reliable means. Detailed standard operating procedures relating to the data recording should be available and the accuracy of the records should be checked. If documentation is retained by electronic data processing methods, only approved personnel should be able to enter or modify data in the electronic data processing systems. There should be records of changes and deletions. Access to the electronic data processing system should be restricted by passwords or other means. The entry of critical data should be independently checked by another personnel. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs, or other means. During the period of retention, the data should be readily available.

Documents Required

Specifications

5.9 Specifications should be available for starting materials, packing materials and finished products and should include methods of identification and of quality testing. When applicable, these should also be available for intermediate products or bulk products. Appropriate specifications for water, solvents and reagents (e.g. acids and bases) used in manufacturing processes should be included. The specifications should be approved, signed and dated by the relevant responsible personnel.

Specifications for Starting and Packing Materials

5.10 Specifications for starting materials and primary or printed packing materials should include the following, if applicable:

a. the name of materials and the internal reference number;
b. the reference to a pharmacopoeia or to a standard recognized by the Chinese Medicines Board under the Chinese Medicine Council (if any); and
c. the quality parameters with acceptable limits stated.

Depending on the manufacturer's practice, the following information may be stated on the specifications, such as:

a. the name(s) of the supplier(s) and the producer(s) of the materials;
b. a specimen of printed packing materials;
c. the methods of sampling and testing, or a reference to such procedures;
d. the storage conditions and precautions; and
e. the maximum period of storage before rechecking.

Packing materials should conform to the requirements of their specifications and should be compatible with the proprietary Chinese medicines they contain. The packing materials should be checked for critical and major physical defects as well as for correctness of identity markings.

5.11 As different starting materials have different stabilities, all test procedures should state the required frequency for retesting each starting material.

Specifications for Intermediate Products and Bulk Products

5.12 Specifications for intermediate products and bulk products should be established if they are acquired from purchase or to be dispatched, or if quality data obtained from the intermediate products would be used in the evaluation of the finished product. The specifications should be similar to the specifications for starting materials or for finished products, as appropriate.

Specifications for Finished Products

5.13 Specifications for finished products should include:

a. the name of the finished product and the reference number (if any);
b. the name(s) of the active ingredient(s);
c. the complete formula;
d. the dosage form and package details;
e. the methods of sampling and testing or a reference to such procedures;
f. the quality parameters with acceptable limits stated;
g. the storage conditions and precautions (if any); and
h. the shelf-life.

Master Formulae

5.14 Master formula should be set out for each product and the batch size to be manufactured.

5.15 The master formula should include:

a. the name of the product, with a reference number of its specifications;
b. the dosage form, the content of each dosage form and the batch size of product;
c. the names of all starting materials (including materials that may disappear during the course of process) to be used in the production process, with the amount of each, and references to the materials;
d. the expected final yield with acceptable limits stated, and relevant intermediate product yields (if any);
e. the areas for producing products and the principal equipment to be used;
f. the methods, or reference to the methods, of preparing the critical equipment for its use, for example, cleaning (especially when the manufacturer changes the product to be produced), assembling, calibrating and sterilizing;
g. a detailed description of the production process, for example, checks on materials, pre-treatment of materials, sequence for adding materials, mixing times, and temperatures;
h. the instructions for in-process controls with their acceptable limits stated;
i. where necessary, the requirements for storage of the bulk products, (including the container, the labelling and any special storage conditions); and
j. any special precautions needed to be observed.

Packing Instructions

5.16 Formally approved packing instructions should be available for each finished product, its pack size and type. These should normally include:

a. the name of the finished product;
b. the dosage form, the content of each dosage form and the method of application;
c. the pack size, expressed in terms of the number, weight or volume of the product in the final container;
d. a list of the packing materials required for packing a batch of finished products including names, quantities, sizes and types, with the reference number relating to the specifications for each packing material;
e. where appropriate, specimens or reproduction of the relevant printed packing materials, indicating where the batch number and expiry date of the product have been marked;

f. special precautions to be observed, including a careful check of the packing area and packing equipment in order to ascertain clearance before packing processes begin;
g. a description of the packing process, including any significant subsidiary processes, and the equipment to be used; and
h. instructions for sampling, and details of in-process controls with acceptable limits stated.

Batch Production Records

5.17 A batch production record should be kept for each batch of product. It should be set out according to the relevant parts of the currently approved master formula. The method of preparing such records should be designed to avoid errors of transcription.

Before any production process begins, a check should be made to determine if previous products, documents or materials not required for the planned production process have been cleared and if the equipment is clean and suitable for use.

Records should be made at the time each action is taken during the course of production and, after completion, the record should be signed and dated by the person responsible for the production process.

Batch production records should include:

a. the name of the product;
b. the batch number of the product;
c. the dates and times of commencement of critical production processes, and of completion of production;
d. the name of the person responsible for each production process;
e. the names of the operators engaged in the critical production processes and, of the person(s) who checked each of these processes (if any);
f. the batch number and/or test control number and the quantity of each starting material (including recovered or reprocessed material) added during the course of production;
g. any relevant production process or event and the major equipment used;
h. the in-process controls performed, the results obtained and the names of the persons carrying them out;

i. the amount of products obtained at different and pertinent production processes (the yield) together with comments or explanations for significant deviations from the expected yield; and
j. notes on special problems including details, with signed approval for any deviation from the master formula.

Batch Packing Records

5.18 A batch packing record should be kept for each batch or part of a batch, of finished products. It should be set out according to the relevant parts of the packing instructions The method of preparing such records should be designed to avoid errors of transcription.

Before any packing process begins, a check should be made to determine if previous products, documents or materials not required for the planned packing process have been cleared and if the equipment is clean and suitable for use.

Records should be made at the time each action is taken during the course of packing and, after completion, the record should be signed and dated by the person responsible for the packing process.

Batch packing records should include:

a. the name of the finished product; the name, batch number and quantity of the bulk product to be packed; the batch number, and the planned quantity of finished product that will be obtained; the quantity actually obtained; and any reconciliation;
b. the date(s) and time(s) of the packing process;
c. the name of the person responsible for the packing process;
d. the names of the operators engaged in the critical packing processes;
e. the checks made for identity and conformity with the packing instructions, including the results of in-process controls;
f. details of the packing process, including equipment and the packing lines used and, when necessary, the instructions for keeping the bulk products unpacked, or a record of returning bulk product that has not been packed to the storage area;
g. whenever possible, samples of the printed packing materials used, including specimens bearing the batch number, expiry date and any additional overprinting;
h. notes on any special problems, including details of any deviation from the packing instructions, with signed approval; and

i. the quantities and reference numbers of printed packing materials and bulk product issued, used, destroyed and returned to stock, and the quantities of finished product obtained to permit an adequate reconciliation.

Standard Operating Procedures (SOPs) and Records

Receipts

5.19 There should be standard operating procedures and records for the receipt of starting material and primary or secondary packing material.

5.20 The records of the receipt of materials should include:

a. the name of the material on the delivery note and the containers;
b. the "in-house" name and/or reference number of material, if different from (a);
c. the date of the receipt of materials;
d. the supplier's name and, the producer's name (if any);
e. the batch number or reference number assigned by the supplier/producer;
f. the total quantity and number of containers received;
g. the batch number assigned after receipt; and
h. any relevant comment (e.g. state of the containers).

5.21 There should be appropriate standard operating procedures for the internal labelling, quarantine and storage of starting materials, packing materials, and other materials.

5.22 Standard operating procedures should be available for each instrument and piece of equipment and placed in close proximity to the instrument or equipment.

Sampling

5.23 There should be standard operating procedures for sampling which specify the person(s) approved to take samples, the methods of sampling and equipment to be used, and any precautions to be observed, to prevent contamination of the materials and products, or any deterioration in their quality (please refer to Chapter 8 "Quality Control").

Batch Numbering

5.24 There should be a standard operating procedure describing the details of the batch numbering system, to ensure that each batch of materials, intermediate products, bulk products or finished products is identified with a unique batch number.

5.25 The batch numbering system should ensure that batch numbers allocated to the products from respective manufacturing processes are related to each other.

5.26 The batch numbering system should ensure that the same batch number would not be repeatedly used. This also applies to batch number of reprocessed product.

5.27 For each batch number allocation, the date of allocation, product name and batch size should be recorded in a logbook.

Testing

5.28 There should be procedures for testing materials and products, with descriptions of the test methods and equipment to be used. The test results should be recorded (please refer to Chapter 8 "Quality Control").

Others

5.29 There should be standard operating procedures for the release and rejection of materials and products. Standard operating procedures should be available for authorized person to release finished product for sale.

5.30 Sales records should be maintained for each batch of product, to facilitate the recall of the batch, if necessary.

5.31 Standard operating procedures and associated records of measures taken, or conclusions reached, should be available for:

a. equipment assembly and validation;
b. test instrument and calibration;
c. clearing of workplace and equipment which had been used for manufacturing products of previous batch, maintenance, cleaning and disinfection;
d. personnel matters including qualification, training, clothing and hygiene;
e. environmental monitoring;
f. pest control;
g. complaints handling;
h. product recalls; and
i. returned products handling.

5.32 There should be cleaning procedures, which describe the responsibilities of all personnel involved in maintaining sanitation, cleaning schedules, cleaning methods, equipment and agents used for cleaning, and the facilities and tools to be cleaned. These procedures should be strictly enforced.

5.33 Logbooks should be kept for major and critical equipment to record any validations, calibrations, maintenance, cleaning or repair operations, including dates and signature(s) of the person(s) who carried out these operations.

5.34 The use of major and critical equipment, and the manufacturing areas where products have been processed, should be recorded according to chronological order of the manufacturing processes.

Chapter 6 Manufacture

Principle

Manufacturing processes must follow clearly defined procedures and comply with the principles of GMP and the conditions stated in the manufacturer licence in proprietary Chinese medicines, to ensure that products of the requisite quality are obtained.

General

6.1 All handling of materials and products, such as receipt, quarantine, sampling, storage, labelling, dispensing, production, packing and distribution, should be done in accordance with procedures or instructions and, where necessary, recorded.

6.2 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled.

6.3 Damage to containers and any other problem that might adversely affect the quality of material should be recorded, and reported to the quality control department for investigation.

6.4 All incoming materials and finished products should be stored in quarantine area immediately after receipt. They should be released for use or distribution only after approval is given by the quality control department.

6.5 Intermediate products and bulk products should be handled on receipt as though they were starting materials.

6.6 All materials and products should be stored under the appropriate conditions established by the manufacturer, and in a way which permit batch segregation for the storage of materials and products, and stock rotation on a “first-in, first-out” or “first-expired, first-out” basis for the release of materials and products.

6.7 Checks on yields and reconciliation of quantities of materials and products should be carried out as necessary to determine whether there are discrepancies beyond the acceptable limits.

6.8 The manufacture of different products should not be carried out simultaneously or consecutively in the same area, unless adequate measures have been taken to prevent any risk of mix-up or cross-contamination.

6.9 In every manufacturing process, measures should be taken to protect products and materials from microbiological and other contamination.

6.10 While handling dry materials and products, special measures should be taken to prevent the generation and dissemination of dust.

6.11 During the course of manufacture, all manufacturing areas, major items of equipment, containers of materials and bulk containers, should be labelled with the name of the product or material being processed or stored, its contents (if any) and the batch number. Where applicable, the labelling should also state the manufacturing process.

6.12 Labels applied to containers, equipment or manufacturing areas should be unambiguous, using the format prescribed by the manufacturer. In addition to the wording on the labels, colours can also be used to indicate the status of materials, equipment or manufacturing areas, such as quarantined, released, rejected, cleaned, etc.

6.13 Checks should be carried out to ensure that pipelines, and equipment used for the transportation of products, are connected in the correct manner.

6.14 Any operation deviated from the instructions or procedures should be avoided. If such operations have to be carried out, they should be approved in writing by a designated person, with the approval from the quality control department, where appropriate.

6.15 Access to manufacturing areas should be restricted to approved personnel.

6.16 Normally, the use of the same areas and equipment for manufacture of proprietary Chinese medicines, and of medicines not classified as proprietary Chinese medicines, should be avoided.

Measures to Prevent Cross-contamination and Bacterial Contamination during the course of manufacture

6.17 Contamination of a starting material or a product by another starting material or product should be avoided during the course of manufacture. Cross-contamination can arise from the release of dust, gases, vapours, sprays or organisms from starting materials and products, from residues on equipment, from intruding insects and from substances shed from personnel's clothing and skin, etc. The significance of this risk varies with the types of contaminant and of the product being contaminated. The most hazardous contaminants are highly sensitizing materials and biological preparations (such as living organisms, certain hormones, cytotoxic substances and other highly active substances). Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds, and those given in large doses and/or over a long time.

6.18 Cross-contamination should be prevented by appropriate technical or organizational measures, for example:

a. providing appropriate airlocks, pressure differentials and air extraction;
b. minimizing the risk of contamination by preventing the re-entry or recirculation of untreated, or insufficiently treated, air;
c. wearing protective clothing when products with contamination likely to be most significant are manufactured;
d. using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
e. using a "closed system" for manufacturing product;
f. preventing herbal medicines, or processed herbal medicines, from making direct contact with the floor;
g. strengthening the measures to prevent cross-contamination when products with toxic herbal medicines are manufactured;
h. using running water to wash screened herbal medicines, or processed herbal medicines. Used water must not be re-used. Different herbal medicines, or processed herbal medicines, must be washed separately;
i. avoiding drying washed herbal medicines or processed herbal medicines under conditions of exposure to weather;
j. checking residues on equipment;
k. establishing a labelling system to indicate the cleanliness status of equipment;
l. undergoing periodic microbiological monitoring in areas where products in which contamination is likely to be most significant, are manufactured; and

m. using water used in the manufacturing process that complies with the requirements of its specifications, and testing the water quality at defined intervals, with reference to the validation results of the water system. The test results should be recorded.

6.19 Measures taken to prevent cross-contamination and their effectiveness should be checked periodically according to standard operating procedures.

Starting Materials

6.20 The purchase of starting materials is an important operation that should involve personnel having particular and thorough knowledge of the starting materials and material suppliers. Starting materials should be purchased in accordance with the requirements of their specifications. Suppliers should be able to supply materials of a consistent quality.

6.21 Starting materials should be purchased only from designated suppliers or from their producers. A quality certificate issued by the material producer with precise details of the quality of the starting materials must be available. The specifications, handling, labelling and packing requirements, as well as complaints handling and rejection procedures of starting materials, should be established by the manufacturer and the suppliers. If the supplier is not able to provide a quality certificate issued by the producer, the manufacturer should be responsible for testing the starting materials, to ensure that the requirements of their specifications are complied.

6.22 For each receipt of starting materials, the integrity and seal of the packages should be checked, as well as the correspondence between the order, the delivery note and the containers' labels.

6.23 If a delivery of material is made up of different batches, each batch should be considered as separate for sampling, testing and release.

6.24 Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

a. the name of starting materials and the internal reference number (where applicable);
b. the batch number(s) given by the supplier and any identification number(s) given by the manufacturer on receipt;

c. the status of the starting materials (e.g. on quarantine, on test, released, rejected)(where appropriate);
d. an expiry date or a date beyond which retesting is necessary (where appropriate);
e. the quantities; and
f. when the starting materials are herbal medicines or processed herbal medicines, the label should also indicate the place of cultivation, place of origin and date of collection or processing (where applicable).

If computerized systems are used throughout to record the storage information of starting materials, not all of the information listed above needs to be indicated on the label.

6.25 The frequency for retesting of starting materials should be stated in the test procedures, having regard to the stability of the starting materials.

6.26 Containers storing toxic herbal medicines, or processed herbal medicines and materials presenting special risks of fire or explosion, should be clearly labelled.

6.27 There should be appropriate procedures or measures to ensure that the starting materials in each container have been identified. Bulk containers, from which samples have been drawn, should be indicated.

6.28 Only starting materials released by the quality control department and within their shelf-life should be used.

6.29 Herbal medicines should be screened, sorted, cut, scraped, processed and washed according to prescribed procedures, before being released for use. During moistening, the herbal medicines should be moistened thoroughly with an adequate amount of water.

6.30 Starting materials should be accurately weighed or measured, and issued only by designated personnel according to prescribed procedures. The materials issued should be stored into clean and properly labelled containers.

6.31 Each starting material issued, and the weight or volume of it, should be checked independently, and recorded.

6.32 Starting materials used for producing a batch of the product should be kept together and conspicuously labelled as such.

Production Processes: Intermediate Products and Bulk Products

6.33 Before any production process is started, the manufacturing area and equipment should be checked to ensure that these are clean and free of any starting materials, products, product residues, labels or documents not relevant to the current production process.

6.34 Intermediate products and bulk products should be stored under appropriate conditions.

6.35 The critical manufacturing process should be validated (please refer to Chapter 7 "Validation").

6.36 Any necessary in-process controls and environmental monitoring should be carried out and recorded.

6.37 If the actual yield significantly deviated from the expected yield, it should be recorded and investigated.

Packing Materials

6.38 The purchase, handling and quality control of primary packing materials and printed packing materials should make reference to the provisions for starting materials.

6.39 Printed packing materials should be stored in separate conditions to prevent access by personnel without approval. Cut labels and other loose printed packing materials should be stored and transported in separate closed containers, to avoid mix-ups. Packing materials should be accurately issued for use only by designated personnel, following the procedures and requirements of packing instructions.

6.40 Each batch of primary packing materials or printed packing materials should be given a specific reference number or identification mark.

6.41 Outdated or obsolete primary packing materials or printed packing materials should be destroyed and their disposal recorded.

Packing Processes

6.42 When the packing processes are being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packed in close proximity unless proper segregation measures or electronic surveillance system are employed.

6.43 Before any packing process is started, the work area, packing lines, printing machines and other equipment should be checked to ensure that these are clean and free of any products, materials or documents not relevant to the current packing process. This line clearance should be performed according to an appropriate checklist and recorded.

6.44 Upon receipt by the packing department, bulk products and packing materials should be checked on their quantity, identity and for their conformity with the packing instructions.

6.45 The name and batch number of the product being handled should be displayed at each packing station or line.

6.46 Primary packing materials should be cleaned before the packing processes. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

6.47 Filling and sealing should be followed as quickly as possible by labelling. If labelling is delayed, appropriate procedures should be made to prevent mix-ups or mislabelling.

6.48 The accuracy of any printing operation (e.g. the printing of batch numbers or expiry dates) done separately, or during the course of packing, should be checked and recorded. Attention should be paid to manual printing, which should be rechecked at regular intervals.

6.49 Special care should be taken when cut labels are used and when overprinting is carried out off-line and during hand-packing operations. Generally speaking, roll-feed labels are preferable to cut labels to avoid mix-ups. On-line checking of all labels by an electronic surveillance system can be helpful in preventing mix-ups. However, it should ensure that any electronic code readers, label counters or similar devices are operating properly.

6.50 Printed and embossed information on packing materials should be clear and resistant to fading or erasing.

6.51 On-line control of the product, during the course of packing, should at least include checks on:

a. the general appearance of the packages;
b. whether the packages are complete;
c. whether the correct bulk products and packing materials are used;
d. whether any printing is correct (e.g. batch numbers or expiry dates); and
e. the correct functioning of line monitors of any electronic surveillance system used (where appropriate).

Samples taken away from the packing line should not be returned.

6.52 Unusual events during the course of packing should be checked and investigated by designated personnel. Products that have been involved in the events should be reintroduced into the packing line only upon approval by a designated personnel. Detailed records should be kept in such events.

6.53 Any significant discrepancy observed during reconciliation of the amount of bulk products, printed packing materials and finished products should be investigated and satisfactorily accounted for, before release of the finished products.

6.54 Upon completion of a packing process, any unused batch-coded printed packing materials should be destroyed, and the destruction recorded. Procedures should be followed, if uncoded printed packing materials are returned to storage area.

Finished Products

6.55 Finished products should be stored in quarantine area before their final release, and should be stored under conditions as established by the manufacturer.

6.56 The evaluation of finished products, and the documentation necessary for release of products for sale, are described in Chapter 8 “Quality Control”.

Rejected and Recovered Materials and Products

6.57 Rejected materials and products should be clearly marked as such and stored separately, in restricted areas. They should be returned to the suppliers, reprocessed or destroyed. These arrangements should be approved by a designated personnel and recorded.

6.58 There should be exceptional justifications for reprocessing the rejected products. Reprocessing should not affect the quality of the final product. The risk of an adverse effect on the quality of the product should be evaluated before reprocessing. Reprocessing should be performed in accordance with a defined and approved procedure. Manufacturing records of the reprocessed products should be kept. The reprocessed products should meet the requirements of their specifications and be given a new batch number.

6.59 The introduction of all, or part, of previous batches of the required quality into a batch of the same product at a defined manufacturing process should be approved in advance. The risk of an adverse effect on the quality of the product (including any possible effect on shelf-life) should be evaluated before recovery. The recovery should be performed in accordance with a defined procedure, and should be recorded.

6.60 The need for additional tests of any finished product that has been reprocessed, or into which a recovered product has been incorporated, should be considered by the quality control department.

Returned Products

6.61 Products returned from the market should be destroyed unless it is certain that their quality complies with the requirements. They may be considered for re-sale, relabelling or introducing into a subsequent batch only after they have been critically assessed by the quality control department in accordance with a written procedure. The nature of the product; any special storage conditions required; its conditions and history, and the time elapsed since it was released should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for release again or recovery, although the active ingredient of the products may be recovered. Arrangements on handling of returned products should be appropriately recorded.

Waste Materials

6.62 Waste materials awaiting disposal should be properly and safely stored. Toxic and inflammable materials should be stored in separate and enclosed cupboards.

6.63 Waste materials should not be allowed to accumulate, so as to maintain sanitation of the premises. They should be stored in suitable containers and removed to waste collection points, in a safe manner, at regular intervals.

Miscellaneous

6.64 Rodenticides, insecticides, fumigating agents and sanitizing agents should not be permitted to contaminate equipment, starting materials, packing materials, intermediate products, bulk products or finished products.

Chapter 7 Validation

Principle

Validation is a fundamental part of GMP. It is the documented act of proving that any procedure, manufacturing process, equipment, material, activity or system actually leads to the expected results. Validation should be conducted in accordance with pre-defined protocols. A written report summarizing the results and conclusions of validation should be prepared and kept. Manufacturing processes and procedures should be established on the basis of validation, and should undergo periodic revalidation to ensure that they remain capable of achieving the intended results. Particular attention should be accorded to the validation of manufacturing processes, test procedures and cleaning procedures.

General

7.1 Validation should include installation, operation and performance qualifications of premises, facilities and equipment, and product validation.

7.2 Critical manufacturing processes should be validated, prospectively or retrospectively.

7.3 When any new master formula or new method of manufacture is adopted, validation should be taken to demonstrate its suitability for routine manufacture. This can ensure that under the defined manufacturing process and using the specified materials and equipment, products can be consistently manufactured of the requisite quality.

7.4 Significant amendments to manufacturing process, including any change in the equipment or materials that may affect product quality and/or the reproducibility of the process, should be validated.

Chapter 8 Quality Control

Principle

Quality control is concerned with sampling, making specifications and testing, and with the organized system, documentation and release procedures, which ensure that the necessary and relevant tests are actually carried out and that only materials and products with satisfactory quality are released for use, and for sale or supply respectively. Quality control is not confined to laboratory operations. It must be involved in all decisions that concern the quality of the product. The independence of the quality control department from the manufacturing department is vital.

General

8.1 Each licensed proprietary Chinese medicines manufacturer (except for a manufacturer performing contract manufacture only, please refer to Chapter 9 "Contract Manufacture and Test") should have a quality control department. The independence of the quality control department from manufacturing department is considered fundamental. The quality control department should be independent of other departments, and be under the management of a person with appropriate qualifications and experience, who has access to one or several quality control laboratories at his or her disposal. Adequate resources must be available to ensure that all the quality control operations are effectively and reliably carried out.

8.2 The principal duties of the head of the quality control department are described in section 2.7. The quality control department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures; to store, evaluate and maintain the quality of the reference standards; to ensure the correct labelling of containers of materials and products; to monitor the stability of the active ingredients and products; to investigate complaints related to the quality of products, and to monitor the environment. All these duties should be carried out in accordance with written procedures and, where necessary, recorded.

8.3 The assessment of finished products should embrace all relevant factors, including the manufacturing conditions; the results of in-process control; the manufacturing (including packing) documentation; compliance with the requirements of specifications for the finished product, and a check on the finished product.

8.4 Quality control personnel must have access to manufacturing areas for sampling and necessary investigation.

8.5 Reference materials, relevant to the tests carried out, should be available in the quality control laboratory.

8.6 Each specification should be approved by the quality control department. The contents required in the specifications for starting materials, intermediate products, bulk products and finished products are referred to sections 5.10 to 5.13.

8.7 The specifications may be revised regularly to comply with the latest edition of the appropriate pharmacopoeias or standards recognized by the Chinese Medicines Board under the Chinese Medicine Council.

Documentation

8.8 Quality control documentation should follow the requirements set out in Chapter 5 "Documentation". The quality control department should maintain the following documents:

a. specifications;
b. sampling procedures;
c. test procedures and records (including test worksheet and/or laboratory notebooks);
d. test reports and/or quality certificates;
e. data from environmental monitoring, when required;
f. validation records of test methods (if any);
g. procedures for, and records of, the calibration of instruments; and
h. procedures for, and records of, the maintenance of equipment.

Sampling

8.9 Samples should be taken in accordance with the approved procedure and should be representative of the batches of material or product.

8.10 Sampling instructions should include:

a. the method of sampling and the sampling plan;
b. the equipment to be used;
c. any precautions to avoid contamination or any deterioration in quality of the materials or products;

d. the amount of sample to be taken;
e. instructions for any required subdivision of the sample;
f. the type of sample container to be used for normal sampling or for aseptic sampling; and
g. any specific precautions to be observed, especially in regard to the sampling of sterile or toxic materials.

8.11 Sampling should be carried out in a manner to avoid contamination, or other adverse effects, on the quality of materials or products. The containers which have been sampled should be marked accordingly, and carefully resealed after sampling.

8.12 The contamination, or mix-up of materials or products should be avoided during sampling. All sampling equipment that will have contact with the material or product should be clean. Special precautions are necessary when handling particularly hazardous or potent materials or products.

8.13 Sampling equipment should be cleaned and, if necessary, sterilized before and after use, and stored separately from other laboratory equipment.

8.14 Each sample container should bear a label indicating:
a. the name of the sample;
b. the batch number;
c. the number of the container from which the sample has been taken;
d. the signature of the person who has taken the sample; and
e. the date of sampling.

8.15 Retention samples from each batch of product should be kept for at least two years after the expiry date. Retention samples should be kept in the final package of the product and stored under the conditions recommended by the manufacturer. If the package of the product is exceptionally large, the product may be divided into smaller samples which are stored in appropriate containers. Retention samples should be of a size sufficient to permit at least two full retests.

8.16 If the active ingredients are stable, samples of active ingredients should be retained for at least two years beyond the release for sale of the corresponding products. Other stable starting materials (other than solvents, gases and water) should be retained for a minimum of two years. If the materials are unstable, this period may be shortened according to their stability, as mentioned in the relevant specifications. Retention samples should be of a size sufficient to permit at least two full retests.

Test Requirements

8.17 Test procedures should be validated in the context of the available facilities and equipment before use.

8.18 Materials or products should be tested according to relevant test procedures. The test results should be checked by the head of the quality control department before he or she decides on the release, or rejection, of the materials or products.

8.19 Test records should include at least the following:

a. the name of the material or product and, the dosage form (if any);
b. the batch number of the material or product and, where appropriate, the name of producer and/or supplier;
c. references to the relevant specifications and test procedures;
d. test results, including observations and calculations, and any prescribed requirements of specifications (limits);
e. dates of tests;
f. the names of the persons who performed the tests;
g. the names of the persons who verified the test results and the calculations (where appropriate); and
h. a clear statement of release, rejection or other status of the product or material, made by the designated responsible person, and bearing his or her signature and the date of that signature.

Starting Materials and Packing Materials

8.20 Before releasing starting materials or packing materials, the head of the quality control department should ensure that the materials have been tested for identity and with other quality parameters which comply with the requirements of specifications.

8.21 A test to ensure identity should be conducted on each container of starting material (please refer to section 6.27).

8.22 A microbiological test should be conducted on the powder of herbal medicines, or processed herbal medicines, directly used for manufacturing proprietary Chinese medicines. Limits of microbiological contamination should be established, for control purposes.

8.23 Each batch of printed packing materials (e.g. labels, package inserts, etc), must be checked upon its receipt.

8.24 The manufacturer is exempted from performing tests (except tests required in section 8.21), provided that the manufacturer establishes the reliability of the supplier's test results through periodic validation of the supplier's test results, and through on-site audits of the supplier's capabilities (please refer to sections 12.7 and 12.8). Quality certificates must be originals or certified copies. Quality certificates must contain the following information:

a. the name of the person who issues the certificate, the signature of the competent official and his or her qualifications;
b. the name and batch number of the material, or product, tested;
c. specifications and test methods; and
d. test results and the date of test.

Finished Products

8.25 Before release, the test results of each batch of finished product should comply with the requirements of specifications for the finished product.

8.26 Only finished products that meet the requirements of specifications can be released. For rejected finished products, reprocessing may be performed but the reprocessed finished products should be ensured to meet the requirements of their specifications, prior to their release.

In-Process Control

8.27 In-process control records should be maintained, and should form part of the batch records.

Batch Record Review

8.28 Batch records and quality control records should be examined. When any discrepancy in the manufacturing process or failure of a product in meeting the requirements of its specifications is identified, other batches of the same product and other associated products should be investigated, if necessary. The results of such investigation, the conclusion, and any follow-up action should be recorded.

Stability Tests

8.29 The quality control department should evaluate the quality and stability of finished products and, when necessary, the quality and stability of starting materials and intermediate products.

8.30 The quality control department should establish the expiry dates and shelf-life of products on the basis of the results of stability tests related to storage conditions.

8.31 A programme for on-going stability tests should be developed and implemented. The programme should include elements such as:

a. a complete description of the product;
b. the methods and parameters of the tests on the quality and physical characteristics of the products and documented evidence that these tests can reliably indicate stability of the products;
c. the number of batches to be tested;
d. the test schedule for each product;
e. the special storage conditions;
f. the quantity of the retention samples; and
g. a summary of all the data generated, including the evaluation and the conclusions of the test.

8.32 Stability of products should be determined prior to marketing or following any significant changes that may affect their stability.

Reagents and Culture Media

8.33 The date of receipt, or preparation, of all reagents and culture media should be recorded.

8.34 Reagents should be prepared according to procedures, and appropriately labelled. The label should indicate the concentration, standardization factor, shelf-life, re-standardization due date, and the storage conditions of the reagents. The label should be signed and dated by the person preparing the reagent.

8.35 Both positive and negative controls should be applied to validate the suitability of culture media. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

Reference Standards

8.36 For reference standards, the label or accompanying document should indicate concentration, date of manufacture, expiry date, the date that the closure is first opened, and storage conditions, where appropriate.

8.37 Reference standards may be available in the form of official reference standards. Reference standards prepared in-house should be tested, released and then stored in the same way as official referene standards. They should be kept under the responsibility of a designated person, in a secure and segregated area.

8.38 Official reference standards should be used only for the purpose described in the appropriate standard.

8.39 Secondary or working standards should be checked at regular intervals to ensure standardization. The secondary or working standards should be standardized on the basis of official reference standards (if any).

8.40 All reference standards should be stored, and used, in a manner that will not adversely affect their quality.

Chapter 9 Contract Manufacture and Test

Principle

When a manufacturer contracts out the manufacture of a product to another manufacturer or contracts out the tests of materials or products to a test organization, the contract manufacture and test must be clearly defined and managed, to avoid any misunderstandings between the parties to the contract that could affect the quality of the product, manufacture operation or tests. There must be a written contract between both parties, which clearly establishes the duties of each party. The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the quality certificate, exercises his or her full responsibility.

General

9.1 Contract manufacture and test, including any proposed changes in technical or other arrangements, should be established in accordance with the product particulars registered with the Chinese Medicines Board under the Chinese Medicine Council.

9.2 There should be a written contract covering the manufacture and/or test arranged under contract and any technical arrangements made in connection with it.

9.3 The contract should authorize the contract giver to audit the facilities of the contract accepter.

9.4 In the case of a contract test, the contract should specify that the final approval for releasing the product for sale must only be given by the authorized person of the contract giver.

The Contract Giver

9.5 The contract giver is responsible for assessing the competence of the contract accepter in successfully carrying out the work required, and for ensuring by means of the contract that the principles of GMP described in these guidelines are followed.

9.6 The contract giver should provide the contract accepter with all the information necessary to carry out the contract work correctly. The contract giver should ensure that the contract accepter is fully aware of any problems associated with the product, work or tests that might pose a hazard to the premises, equipment, personnel, other materials or other products.

9.7 The contract giver should ensure that all products and materials delivered to him or her by the contract accepter have complied with the requirements of their specifications or that the products and materials have been released by the authorized person of the contract accepter.

The Contract Accepter

9.8 The contract accepter must have adequate knowledge and experience; suitable premises and equipment; and competent personnel, to carry out satisfactorily the work commissioned by the contract giver. The contract manufacture can only be undertaken by a manufacturer holding a manufacturer licence in proprietary Chinese medicines.

9.9 The contract accepter should not pass to a third party any work entrusted to him or her under the contract, without the contract giver's prior evaluation and approval of any such arrangements. The contract accepter should ensure that the manufacturing and testing information is made available to any third party in the same way as provided by the original contract giver.

9.10 The contract accepter should prevent causing any adverse affect on the quality of the product manufactured and/or tested for the contract giver.

The Contract

9.11 A contract should be drawn up between the contract giver and the contract accepter specifying their respective responsibilities relating to the manufacture and quality control of the product. Technical aspects of the contract should be drawn up by competent personnel suitably knowledgeable in pharmaceutical technology, testing and GMP. All arrangements for contract manufacture and test must comply with the requirements of the Chinese Medicines Board under the Chinese Medicine Council.

9.12 The contract should specify the ways in which the authorized person releases the product for sale, to ensure that each batch is manufactured in compliance with the requirements of the Chinese Medicines Board under the Chinese Medicine Council.

9.13 The contract should clearly describe the responsibilities of both parties, including responsibilities of purchasing, testing and releasing materials and of undertaking manufacture and quality controls (including in-process controls), and of sampling and testing. In the case of contract test, the contract should state whether the contract accepter take samples at the premises of the contract giver.

9.14 Manufacturing records, test records, sales records and samples should be kept by, or be available to, the contract giver. The assessment of the quality of a product in the event of complaints or of a suspected defect, should be recorded and such records must be accessible to the contract giver. These arrangements should be specified in the procedures for handling defective product or product recall, of the contract giver.

9.15 The contract should specify the way of handling any rejected starting materials, intermediate products, bulk products and finished products. It should also specify the procedures whereby the test organization will notify contract giver, if the tested products are rejected.

Chapter 10 Complaints

Principle

All complaints and other information concerning potentially defective products must be carefully investigated, according to written procedures.

General

10.1 A person responsible for handling the complaints and deciding the actions to be taken should be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter should be made aware of any complaint, investigation or product recall.

10.2 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

10.3 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. Quality control personnel should be involved in such investigations.

10.4 If a product defect is discovered or suspected in a batch of product, consideration should be given to checking other batches of relevant products in order to determine whether their quality has also been affected. In particular, batches which have been reprocessed due to product defect found should be investigated.

10.5 Where necessary, appropriate follow-up action, including product recall, should be taken after investigation and evaluation of the complaint.

10.6 All the decisions and follow-up actions taken as a result of a complaint should be recorded and should be referenced to the corresponding batch records.

10.7 Complaint records should be regularly reviewed to identify any special or recurring problems requiring attention, so as to recall marketed products.

10.8 Where necessary, relevant distributors should be notified of the complaints.

10.9 The Chinese Medicines Board under the Chinese Medicine Council should be notified in case of any faulty manufacture, product deterioration or any other serious quality problems of a products.

Chapter 11 Product Recalls

Principle

There should be a product recall system to recall from the market, promptly and effectively, products known or suspected to be defective. When necessary, the Chinese Medicines Board under the Chinese Medicine Council may instruct the manufacturer to recall products.

General

11.1 A person responsible for the execution and coordination of product recalls should be designated, to be supported by adequate staff, to handle the recalls, having regard to the emergency of the situation. This person should be independent of the sales and marketing departments. If this person is different from the authorized person, the latter should be made aware of any aspects of product recalls.

11.2 There should be established written procedures for product recall, and they should be regularly reviewed and revised. Through the recall system, recall should be capable of being initiated promptly, down to the level of the medical institutions, medical practitioners and retail outlets.

11.3 The Chinese Medicines Board under the Chinese Medicine Council should be notified before the product recall starts.

11.4 When a product recall is conducted, the relevant customers and consumers should be notified promptly of the arrangements.

11.5 During a product recall, the Chinese Medicines Board under the Chinese Medicine Council should be regularly informed of the progress of the recall, including detailed descriptions of quantities of products sold and recalled, to enable an evaluation of the effectiveness of the product recall to be conducted.

11.6 Local, mainland or overseas product suppliers and customers should be notified of the recall of defective or suspected to be defective products.

11.7 The competent authorities of all countries or regions to which the given products may have been distributed should be promptly informed of the recall of defective or suspected to be defective products.

11.8 For each batch of product, there should be sales records. The sales records should be readily available to the personnel responsible for recalls, to enable them to conduct the recall effectively. The records should contain sufficient information on wholesalers and customers directly supplied with the products (with addresses, phone and/or fax numbers inside and outside working hours, product names, batch number of the product and quantities of product sold). The same arrangement is applicable to exported products, samples for clinical tests and medical samples.

11.9 The progress of the recall should be recorded and a final report made, including reconciliation between the sold and recalled quantities of the product.

11.10 The effectiveness of the recall should be evaluated regularly.

11.11 An instruction should be given to store recalled products in a secure and segregated area, while their fate is being decided.

Chapter 12 Self-Inspection and Quality Audits

Principle

The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP requirements in all aspects of manufacture and quality control. Through the self-inspection programme, a manufacturer should be able to detect any items that do not meet the GMP requirements, and to recommend the corrective measures. Self-inspection should be performed routinely and may, in addition, be performed on special occasions, for example, after product recalls or repeated product rejections, or when an inspection by pharmacist inspectors appointed by the Chinese Medicines Board under the Chinese Medicine Council is being conducted. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommended corrective measures should be implemented by the manufacturer. The procedures for self-inspection should be documented, and there should be an effective follow-up programme.

Items for Self-Inspection

12.1 Written instructions for self-inspection should be established and the minimum and uniform standards of the requirements should be stated. The written instructions should include questionnaires on GMP requirements covering at least the following items:

a. personnel;
b. premises (including personnel facilities);
c. maintenance of premises and equipment;
d. storage of starting materials and finished products;
e. equipment;
f. manufacture and in-process controls;
g. quality control;
h. documentation;
i. sanitation and hygiene;
j. validation and re-validation programmes;
k. calibration of instruments or measurement systems;
l. product recall procedures;
m. complaints handling; and
n. labels control.

Self-Inspection Team

12.2 The management of the manufacturer should appoint a self-inspection team, consisting of staff who are experts in their own fields, and who are familiar with GMP. Suitable persons from outside the organization may be appointed to join the self-inspection team.

Frequency of Self-Inspections

12.3 Manufacturer may determine the frequency of self-inspections, according to need.

Self-Inspection Report

12.4 A report should be made on completion of a self-inspection. The report should include:

a. the self-inspection results;
b. an evaluation and conclusions; and
c. the recommended corrective measures.

Follow-Up Action

12.5 The management of the manufacturer should evaluate both the self-inspection report and the corrective measures, as necessary.

Quality Audit

12.6 It may be useful to supplement self-inspections with a quality audit. A quality audit consists of examination and assessment of all or part of a quality system with the purpose of improving it. A quality audit is usually conducted by outside and independent specialists or by a team specially designated by the management of manufacturer for this purpose. Such audits may also be extended to suppliers and contractors (please refer to Chapter 9 “Contract Manufacture and Test”).

Suppliers’ Audits

12.7 The quality control department has the responsibility, together with other relevant departments, of recommending reliable suppliers for the supply of suitable starting materials and packing materials.

12.8 Before a supplier is included in the specifications, the suppliers' history, and the nature of the materials to be supplied should be evaluated.

Appendix Sterile Proprietary Chinese Medicines

Explanation

This appendix should not be taken to replace Chapters 1 to 12. It supplements special items that should be attended to during the manufacture of sterile proprietary Chinese medicines to minimize the risks of microbiological, particulate and pyrogen contamination.

General

1. As a principle, methods of sterilizing herbal medicines, processed herbal medicines, intermediate products, bulk products and proprietary Chinese medicines should cause no change in the quality.

2. The manufacture of sterile products should be carried out in clean areas. The clean areas should be equipped with airlocks, through which personnel and/or materials can enter clean areas. The clean areas should be maintained to an appropriate grade of cleanliness and equipped with an air purifying system of appropriate efficiency.

3. The preparation of components (such as containers and closures), the product production process, the filling process and the sterilization process of products should each be carried out separately, in different areas within the clean area.

4. Clean areas for manufacturing sterile products are classified according to the required characteristics of the air, in grades A, B, C, and D (please refer to Table 1).

5. The manufacture of each category of sterile product requires an appropriate grade of air cleanliness to minimize the risks of particulate or microbiological contamination of the product or materials. Sections 7 to 10 of this appendix specify the minimum requirements of different sterile products on the air cleanliness grades in the manufacturing environment (please refer to Table 2). The particulate and microbiological conditions specific in Table 1 should be maintained in the zone immediately surrounding the product, whenever the product is exposed in the clean area. These conditions should be achieved throughout the environment even if no personnel are present in the clean area. If such conditions cannot be achieved, the clean area should be cleaned thoroughly to comply with the conditions.

Table 1: Air cleanliness grades of clean areas.

Cleanliness Grade	Maximum number of particles permitted per cubic metre		Maximum number of viable microorganisms permitted per cubic metre
	≧0.5 μm	≧5 μm	
A (Laminar air flow work station)	3, 500	None	< 1
B	3, 500	None	5
C	350, 000	2, 000	100
D	3, 500, 000	20, 000	500

Notes:

a. Laminar air flow work station should provide a homogeneous air speed of about 0.30 m/s for vertical flow and about 0.45 m/s for horizontal flow.
b. The number of air changes should generally be higher than 20 per hour with a good air flow pattern and appropriate high-efficiency particulate air filters should be installed in grades B, C and D clean areas.
c. Low values for contaminants are reliable only when a large number of air samples are tested.
d. These guidelines given for the maximum permitted number of particles in different grades corresponds approximately to the United States Federal Standard as follows: Class 100 (grades A and B), Class 10, 000 (grade C), and Class 100, 000 (grade D).
e. It may not always be possible to demonstrate full conformity with air particulate requirements at the point of fill when filling is in progress, owing to the generation of particles or droplets from the product itself.

Manufacture of Sterile Products

6. Sterile products can be divided into three categories: (1) the products sealed in final containers and terminally sterilized; (2) the products sterilized by filtration; (3) the products that can be sterilized neither by filtration nor terminally in final containers and must be manufactured from sterile starting materials in an aseptic environment. Air cleanliness grades as specified in sections 7 to 10 for manufacturing products must be selected by the manufacturer on the basis of validation results of that manufacturing process (e.g. sterile media fills).

Terminally Sterilized Products

7. Solutions should generally be manufactured in a grade C environment to ensure low microbial and particulate counts for immediate filtration and sterilization. A solution could also be manufactured in a grade D environment if additional measures are taken to minimize the risk of contamination, such as the use of closed systems. For parenterals, filling should be done in a laminar air flow work station (grade A environment) in a grade C environment. The production and filling of other sterile products (e.g. creams, ointments, suspensions and emulsions), should generally be done in a grade C environment before terminal sterilization.

Sterile Filtered Products

8. The handling of starting materials and the production of solutions should be done in a grade C environment. These activities could also be done in a grade D environment if additional measures are taken to minimize the risk of contamination, such as the use of closed systems prior to sterile filtration. After sterile filtration, the product must be handled and filled in a grade A or B environment, with a grade B or C background environment respectively.

Sterile Products Manufactured from Sterile Starting Materials in an Aseptic Environment

9. The handling of starting materials and the manufacture of products should be done in a grade A or B environment, with a grade B or C background environment respectively.

Closed Systems

10. The utilization of closed systems and automated equipment in the manufacture of sterile products can minimize human interventions and ensure the sterility of products. When such systems and equipment are used, the recommendations in this appendix, particularly those relating to air quality and monitoring still apply. The terms “work station” and “environment” should be suitably interpreted.

Table 2: Manufacture of sterile products and the corresponding manufacturing environment

Manufacturing Processes	Manufacturing Environment
(1) Terminally Sterilized Products	
a) Manufacture of solutions	Grade C or Grade D with additional measures to minimize the risk of contamination (e.g. use of closed systems)
b) Filling of parenterals	Grade A work station in Grade C
c) Production and filling of other sterile products (e.g. creams, ointments, suspensions and emulsions)	Grade C
(2) Sterile Filtered Products	
a) Handling of starting materials and production of solutions	Grade C or Grade D with additional measures to minimize the risk of contamination (e.g. use of closed systems)
b) Handling and filling of products after sterile filtration	Grade A with Grade B background or Grade B with Grade C background
(3) Sterile Products Manufactured from Sterile Starting Materials in an Aseptic Environment	
Handling of starting materials and manufacture of products	Grade A with Grade B background or Grade B with Grade C background

Personnel

11. Only the minimum number of personnel should be present in clean areas; this is particularly important during the aseptic manufacturing processes. Checks and quality controls should be conducted from outside the areas, as far as possible.

12. All personnel (including those concerned with cleaning and maintenance) working in clean areas should receive regular training in disciplines relevant to hygiene, basic knowledge of microbiology and the correct manufacture of sterile products. When outside personnel who have not received such training (e.g. maintenance contractors of premises or equipment) need to be brought in, particular care should be taken over their supervision.

13. Personnel who have engaged in the processing of animal tissue materials, or of culture media of microorganisms other than those used in the current product manufacture, should not enter clean areas unless rigorous and clearly defined decontamination procedures have been followed.

14. High standards of personal hygiene and sanitation of clean areas must be maintained, and personnel involved in the manufacture of sterile products should be instructed to report any condition that may cause the shedding of abnormal numbers or types of contaminants. Periodic health checks are desirable. A competent personnel should be designated to handle microbiological hazards introduced by personnel.

15. Outdoor clothing and footwear should not be brought into the clean areas, and personnel entering the changing rooms should already be clad in standard factory protective garments. Changing and washing should follow the procedure.

16. Wrist watches and jewellery should not be worn in clean areas, and cosmetics which can shed particles should not be used.

17. The type of clean working clothing and its quality has to be adapted to the requirements of the manufacturing process and the clean area, and worn in such a way as to protect the product from contamination.

18. Clean working clothing should be appropriate to the requirements of the air cleanliness grade of the area where the personnel will be working:

    Grade D: The hair and, beard (where appropriate) should be covered. General protective clothing and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to prevent any contaminants coming from outside the clean area.

    Grade C: The hair and, beard (where appropriate) should be covered. A single or two-piece trouser suit, gathered at the wrists and with a high neck and appropriate shoes or overshoes should be worn. The clothing should shed virtually no fibres or particulate matter.

Grade B: A headgear should totally enclose the hair and, beard (where appropriate); it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets; sterilized, non-powdered rubber or plastic gloves should be worn and clothing sleeves should be tucked into the gloves; sterilized or disinfected footwear should be worn and trouser-bottoms should be tucked inside the footwear. The clothing should shed virtually no fibres or particulate matter and should retain particles shed by the body.

19. For every person working in a grade B clean area, clean sterilized working clothing should be changed at each work session, or at least once a day if monitoring results justify it. Gloves should be regularly disinfected during the course of manufacture, and gloves and masks should be changed at every working session. Disposable clean working clothing may be used when necessary.

20. Clean working clothing worn in a clean area above grade D should be laundered in the clean areas and in such a way that it does not gather additional particulate contaminants which can later be shed. Separate laundry facilities for such clothing are desirable. If clothing is damaged by inappropriate laundry or sterilization, there may be an increased risk of shedding particles. Laundry and sterilization of clothing should follow standard operating procedures.

Clean Areas

21. Clean areas should, as far as possible, be designed to prevent the unnecessary entry of personnel. Grade B clean areas should be designed such that the manufacturing processes are visible from outside.

22. Consideration should be given to preventing unnecessary access to clean areas where a critical filling process is carried out (e.g. grade A filling areas) by the use of a physical barrier.

23. In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to permit their repeated cleaning and disinfection, and to minimize risk of shedding or accumulation of particles or microorganisms.

24. To facilitate cleaning and to reduce the accumulation of dust, there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment in clean areas. Doors in clean areas should facilitate cleaning. Sliding doors should not be used due to the presence of uncleanable recesses.

25. False ceilings should be sealed to prevent the entry of contaminants.

26. Pipes and ducts should be installed so that they do not create recesses which are difficult to clean.

27. Sinks and drains should be avoided wherever possible and must be excluded from clean areas where aseptic manufacturing processes are carried out. Sinks and drains should be designed, located, and maintained to avoid microbiological contamination; they should be fitted with easily cleanable traps with air breaks, to effectively prevent back-flow. Any floor channel should be open, easily cleanable and be connected to drains outside the area in a manner which prevents entry of microbiological contaminants.

28. Changing rooms should be fitted with airlocks to provide separation of the different stages of changing, to minimize the risk of microbiological and particulate contamination of protective clothing. They should be effectively flushed with filtered air. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. Hand-washing facilities should be provided only in the changing rooms, not in areas where aseptic manufacturing processes are carried out.

29. The doors of the airlock should not be opened at a time. The airlock should be equipped with an interlocking system and a visual and/or audible warning system, to prevent more than one airlock door from opening at a time.

30. With an air purifying system, clean areas should maintain a positive pressure relative to the surrounding areas, and be effectively flushed with supplied air. There should be particular protective measures for the exposed environment to which the product and the cleaned components are stored to prevent their contamination. For the areas where highly contaminating, or highly toxic, materials are handled, the air purifying system and the pressure differentials should be adjusted. Decontamination facilities, and filters for the treatment of air leaving a clean area, should be installed in those areas.

31. It should be ensured that air flow patterns do not present a contamination risk, such as air flows distributing particles from persons, manufacturing processes and equipment to manufacturing areas of products in which contamination is likely to be most significant.

32. A warning system should be installed to indicate any failure in the air purifying system. An indicator of pressure difference should be fitted between two adjacent clean areas where measurement is required, and the pressure difference should be regularly recorded.

Equipment

33. A conveyor belt should not pass through a partition between a grade B clean area and a clean area with a lower air cleanliness grade, unless the belt is equipped with a device which can provide sterilization continuously (e.g. in a sterilizing tunnel).

34. Equipment and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean areas. The equipment should be sterilized after reassembly, when necessary.

35. When equipment maintenance is carried out within the clean area, clean and disinfected tools should be used, and the area should be cleaned and disinfected before manufacturing processes recommence, if the required standards of cleanliness and/or asepsis have not been maintained during the maintenance work.

36. The systems of water used in the manufacturing process should be designed, constructed and maintained to ensure the supply of water of an appropriate quality. They should be operated within their designed capacity. Water used in the manufacturing process should be treated, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at 80℃ or at not more than 4℃.

37. All equipment, including sterilizers, air purifying systems, and systems for water used in the manufacturing process (including stills), should have maintenance and validation programme. Written approval for use should be made upon completion of maintenance work of these equipment.

Sanitation

38. The sanitation of clean areas is particularly important. Clean areas should be cleaned frequently and thoroughly in accordance with a cleaning programme approved by the quality control department. Where disinfectants are used, more than one type should be employed, with periodic alterations and the results of such disinfection should be regularly monitored, to prevent the emergence of resistant microbial strains. In view of its limited effectiveness, ultraviolet light should not be used as a substitute for disinfectants.

39. Disinfectants or detergents should be monitored for microbiological contamination; dilutions should be kept in previously cleaned containers and should not be stored for long periods, unless sterilized. Partly emptied containers should not be topped up.

40. Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

41. Clean areas should be monitored regularly during the course of manufacture, by means of microbial counts of air and surfaces. Where aseptic manufacturing processes are performed, monitoring should be frequent to ensure that the environment of the clean areas complies with the requirements. The results of monitoring should be reviewed when products are being considered for release. Air particulate quality should also be evaluated on a regular basis. Monitoring is desirable in certain circumstances, even when there are no manufacturing processes, such as after validation of systems, cleaning and fumigation of the clean areas.

Manufacturing Processes

42. Protective measures to minimize the risk of contamination should be taken during the course of manufacture, including the processes before sterilization.

43. Preparations containing live microbiological organisms should not be produced or filled in areas used for the manufacture of proprietary Chinese medicines. However, vaccines consisting of dead organisms, or of bacterial extracts, may be filled, after validations of inactivation and cleaning procedures, in the same areas as other sterile proprietary Chinese medicines.

44. The use of sterile media fills ("broth fills") in the simulation of aseptic manufacturing processes is a valuable part of an overall validation of an aseptic process. When the aseptic manufacturing processes are simulated, the following requirements should be met:
    a. they should simulate as closely as possible the actual manufacturing processes, such as the complexity of the manufacturing processes, the number of personnel working, and length of time for completing the manufacturing processes;
    b. the sterile medium, or media, selected should be capable of growing a wide spectrum of microorganisms, including those that would be expected to be found in the filling environment; and
    c. several times of sterile media fills should be carried out to give a high degree of assurance that low levels of contamination, if present, could be detected. The target of the simulation should be zero growth and anything above 0.1% of the sterile media found to have microbiological contamination should be considered unacceptable. Any source of microbiological contamination should be investigated.

    Sterile media fill should be repeated regularly and whenever alterations in the clean areas, equipment or aseptic manufacturing process are sufficient to warrant revalidation.

45. Validations should be carried out carefully, to avoid causing any hazard to the manufacturing processes.

46. Water sources, the systems for water used in the manufacturing process and water used in the manufacturing process, should be monitored regularly for chemicals, endotoxins and other biological contamination. This is to ensure that the water used in the manufacturing process complies with the requirements of its specifications. Records should be maintained of the results of such monitoring and of any action taken.

47. Activities of personnel in clean areas, especially those activities when aseptic manufacturing processes are in progress, should be controlled, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The temperature and humidity of clean areas should not be uncomfortably high, because of the nature of the clean working clothing worn.

48. Microbiological contamination of starting materials should be minimal prior to sterilization. The relevant specifications should include the acceptable limit of microbiological contamination. Starting materials should be tested for microbiological contamination, before sterilization.

49. Containers and materials liable to shed fibres should be avoided in clean areas, and should not be used when an aseptic manufacturing process is in progress.

50. Components, bulk product containers and equipment should be handled carefully after the final cleaning process, in such a way that they are not recontaminated. The stage of processing of components, bulk product containers and equipment should be properly identified by appropriate measures.

51. The interval between the washing, drying and sterilization of components, bulk product containers and equipment, as well as between the completion of sterilization and use, should be as short as possible and subject to a time-limit appropriate to the validated storage conditions.

52. The interval between the start of the manufacture of a solution and its sterile filtration should be as short as possible. A maximum permissible interval should be set for each product that takes into account its ingredients and the prescribed method of storage.

53. Purified gas should be used to purge a solution or to blanket a product.

54. Microbiological contamination of products ("bio-burden") should be minimal, before sterilization. There should be an acceptable limit on microbiological contamination immediately before sterilization, which is related to the efficiency of the sterilization method to be used and the risk of contamination by pyrogens. All solutions, in particular large volume parenterals, should be passed through sterile filtration, if possible immediately before the filling process. Where aqueous solutions are filled into sealed containers, any pressure release outlets should be protected, for example, by hydrophobic microbial air filters.

55. Components, bulk product containers, equipment and any other articles required for the aseptic manufacturing process should be sterilized and, wherever possible, passed into the clean area through double-ended sterilizers, to avoid contaminating the clean area or articles. Other procedures which achieve the same end of not introducing contamination (e.g. triple wrapping) may be acceptable in some circumstances.

56. The efficacy of any new manufacturing process should be validated, and revalidated at regular intervals thereafter, or when any significant change is made in the manufacturing process or equipment.

Sterilization

57. All sterilization processes must be validated. Particular attention should be given when the adopted sterilization method is not a standard method, or when a product which is not a simple aqueous or oily solution is sterilized.

58. Sterilization methods include: moist heat sterilization; dry heat sterilization; ethylene oxide sterilization (or using other suitable gaseous sterilizing agent for sterilization); sterile filtration with subsequent aseptic filling; or sterilization by irradiation with ionizing radiation (but not with ultraviolet radiation, unless thoroughly validated). Each method has its particular applications and limitations. Where possible and practicable, heat sterilization is the preferred method.

59. Whenever possible, equipment used for sterilizing should be chosen so that it can undergo effective dry heat, moist heat or other sterilization methods.

60. Before any sterilization process is adopted, its suitability for the product and its efficacy in achieving the desired sterilizing conditions, in all parts of each type of load to be processed, should be validated. The validation should be repeated at least annually, and whenever significant modifications have been made to the equipment. The results of validation should be recorded.

61. Biological indicators should be considered only as an additional measure for monitoring the sterilization process. If biological indicators are used, strict measures should be taken to avoid transferring microorganisms from them to products.

62. Measures should be established to clearly differentiate the products which have not been sterilized from those which have. Each basket, tray, or other carrier of products or components should be clearly labelled with the name of the article, its batch number and an indication of whether or not it has been sterilized. Indicators such as autoclave tape may be used to indicate whether or not a batch (or sub-batch) of product has passed through a sterilization process, but they do not give a reliable indication that the batch is, in fact, sterile.

63. Each sterilization process should be recorded. The assessments of the sterilization record should constitute a part of the product release procedures.

Heat Sterilization

64. Each heat sterilization cycle should be recorded by appropriate equipment with suitable accuracy and precision, for example, the record of sterilizing temperature on a time/temperature chart with a suitable scale. The temperature should be recorded from a probe at the coolest part of the load or loaded chamber, this point having been determined during the validation, and preferably also checked against a second independent temperature probe located at the same position. The time/temperature chart, or a photocopy of it, should form a part of the batch record. Chemical or biological indicators may be used in addition, but should not replace the use of the temperature probe.

65. Sufficient time must be given for the whole of the load to reach the required temperature before measurement of the sterilizing time is started. This time must be determined for each type of load to be sterilized.

66. During the cooling phase of a heat sterilization cycle, measures should be taken against contamination of a sterilized load during cooling. Any cooling gas or fluid in contact with the product should be sterilized.

Moist Heat Sterilization

67. Moist heat sterilization is suitable only for water wettable products or materials and aqueous solutions. Both temperature and pressure should be used as indicators to monitor the moist heat sterilization process. The temperature recorder should normally be independent of the temperature controller, and there should be an independent temperature indicator, the reading from which is routinely checked against the time/temperature chart during the sterilization cycle. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position during the sterilization cycle. There should be regular leak tests on the sterilizer, if a vacuum phase is part of the cycle.

68. The products to be sterilized, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but prevents recontamination after sterilization. All products should be in contact with water or saturated steam at the required temperature for the required time.

69. Measures should be taken to ensure that steam used for sterilization is of a suitable quality and does not contain additives at a level that could cause contamination to the product or equipment.

Dry Heat Sterilization

70. Dry heat sterilization process should include air circulation within the sterilizing chamber, and the maintenance of positive pressure to prevent the entry of non-sterile air. In case air needs to be supplied, it should be passed through a microorganism-retaining filter. Where dry heat sterilization is also intended to remove pyrogens, challenge tests using endotoxins would be required as part of the validation.

Radiation Sterilization

71. Radiation sterilization is used mainly for the sterilization of heat sensitive materials and products. Proprietary Chinese medicines and some packing materials may be radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not an acceptable method for terminal sterilization.

72. During the course of radiation sterilization, the radiation dose received by the product or material itself should be measured by dosimeters which are independent of dose rate. Dosimeters should be inserted in the load in sufficient number, and close enough together to ensure that there is always a dosimeter in the chamber. Where plastic dosimeters are used, they should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period after their exposure to radiation.

73. Biological indicators may be used only as an additional measure of monitoring. Radiation-sensitive colour discs may be used to differentiate between articles that have been subjected to irradiation and those that have not. However, they are not indicators of successful sterilization. The information obtained should be recorded in the batch record.

74. Validation procedures should ensure that consideration is given to the effects of variations in the density of the packages on the efficiency of the sterilization.

75. Materials or products handling procedures should prevent any mix-up between irradiated and non-irradiated materials or products. Each package should carry a radiation-sensitive colour disc, to show whether it has been subjected to radiation treatment.

76. The total radiation dose should be administered within a predetermined time span.

77. If the radiation sterilization process is carried out by an outside contractor, the manufacturer has the responsibility for ensuring that the requirements stated above are met, and that the sterilization process is validated. The responsibilities of the radiation equipment operator (e.g. using right radiation dose) should also be specified.

Ethylene Oxide Sterilization

78. In some cases, other gases and fumigants may be used for sterilization. Ethylene oxide should only be used when no other method is practicable. During sterilization process validation, it should be shown that ethylene oxide has no damaging effect on the products or materials, and that the conditions and time allowed for degassing are such as to reduce any residual gas and reactive products to defined acceptable limits for that type of product or material. These limits should be incorporated into the specifications.

79. Direct contact between gas and microbial cells is essential in ethylene oxide sterilization. Measures should be taken to avoid the presence of organisms likely to be enclosed in material (such as crystals or dried protein). The nature and quantity of packing materials can significantly affect the efficiency of the sterilization process.

80. Before ethylene oxide sterilization, products or materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be minimized.

81. Each sterilization cycle should be monitored with suitable biological indicators, distributed throughout the load. The information so obtained should be recorded in the batch record. Biological indicators should be stored and used according to the producer's instructions, and their performance checked by positive controls.

82. For each sterilization cycle, records should be kept of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber and of the gas concentration. The pressure and temperature should be recorded throughout the cycle, on a chart. These records should form a part of the batch record.

83. After the sterilization cycle, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reactive products to fall to the defined level. This procedure should be validated.

Sterile Filtration

84. Whenever possible, products should be sterilized in the final container, preferably by heat sterilization. Certain liquids and solutions that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size of 0.22 μm (or less), or with at least equivalent microorganism retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds, but not all viruses or mycoplasmas. Consideration should then be given to increasing the efficacy of sterilization with some degree of heat treatment.

85. Because of the potential additional risks of the sterile filtration, when compared with other sterilization methods, a double filter layer, or second filtration via a further sterilized microorganism-retaining filter immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.

86. Fibre-shedding filters should not be used. The use of asbestos-containing filters should be absolutely excluded.

87. The integrity of the filter should be checked by an appropriate method such as a bubble point test before, or immediately after, each use. The time taken to filter a known volume of solution, and the pressure difference to be used across the filter, should be determined during validation. Any significant differences from this should be noted and investigated. Results of these checks should be recorded in the batch record.

88. Each filter should not be used for more than one working day, unless such use has been validated.

89. The filter should not affect the quality of the product, by the removal of ingredients from it, or by release of foreign matters into it.

Containers for Sterile Products

90. Containers should be sealed by appropriately validated methods. Samples should be checked for the sealing, according to appropriate procedures.

91. Containers sealed under vacuum should be sampled and tested for maintenance of that vacuum, after an appropriately predetermined period.

92. Every filled parenteral products should be checked for clarity. When the checking is done visually, it should be done under suitable conditions of illumination and background. The eye-sight of the operators who conduct the checking, should be regularly checked, with spectacles if worn, and the operators should be given frequent breaks from the visual on-line checking. Where other methods and equipment are used to check for clarity, the methods should be validated and the performance of the equipment should be checked at intervals.

93. Returned primary packing materials, which had direct contact with products must not be reused.

Quality Control

94. The sterility test applied to the finished product should be regarded only as the last in a series of measures by which sterility is assured. They can be interpreted only in conjunction with the environmental monitoring records and batch records.

95. A batch of product failing an initial sterility test should not be released on the basis of a retest, unless an investigation into the type of organism, the environmental monitoring records and relevant batch records has been conducted and has shown that the original test was invalid.

96. Samples taken for sterility test should be representative of the whole of the batch. However, they should in particular include samples taken from those parts of the batch considered to be most at risk of contamination, for example:
    a. for products which have been filled aseptically, samples should include products filled at the beginning and end of the batch, and after any significant interruption of filling;
    b. for products which have been heat sterilized in their final containers, consideration should be given to taking samples from the coolest parts of the load.

97. For injectable products, consideration should be given to testing the water used in the manufacturing process, the intermediate product and finished product for endotoxins, according to an established pharmacopoeial method. Test methods should have been validated. When a sample fails these tests, the cause of failure should be investigated and appropriate remedial measures taken.