

Hướng dẫn về GMP (thực hành sản xuất tốt) phát triển bởi ASEAN



ASEAN Guideline on Good Manufacturing Practice for
Traditional Medicines

Disclaimer:

This document is provided for information purpose only and subject to changes, pending the finalisation of the ASEAN Agreement on Regulatory Framework for Traditional Medicines. Official references to this document can only be made once the said Agreement has been finalised.

INTRODUCTION

Good Manufacturing Practice (GMP) is an essential component in the manufacture of Traditional Medicines (TM). The primary objective of GMP is to ensure that the quality requirements of all products are met and consistently maintained to safeguard public health.

Manufacture is defined as:

- (a) the making or assembling of the finished product,
- (b) the enclosing or packing of the finished product in any container in a form suitable for administration or application, and the labelling of the container, and
- (c) the carrying out of any process in the course of any of the foregoing activities.

Good Manufacturing Practices shall be implemented in the manufacture of Traditional Medicines, such that there is overall control to ensure the consumer receives good quality of product for its intended use. Haphazard operations shall not be permitted in the manufacturing processes of finished products.

Recognising that there are similar GMP guidelines that are in existence and used internationally and by NRAs with international obligation, this document aims to provide guidance for good manufacturing practices. Whilst these guidelines are not intended to place any restraint for the development of new concepts or new technologies, where needed, justifications shall be provided to demonstrate that innovative measures proposed or to be implemented are able to provide equivalent or better controls over the quality system and manufacturing process. Importantly, the safety and quality of traditional medicines must be assured while using measures other than those described in these guidelines.

The starting materials used in the production of traditional medicines are often natural in origin. These materials, such as plants and animal parts, are prone to contamination, deterioration and variation in quality. Therefore, the control of the starting materials, storage and processing of traditional medicines is important. The control is also required because of the often complex and variable nature, the number and the small quantity of defined active materials in many traditional medicines.

Materials such as animal parts may spread undesirable disease (e.g. Transmissible Spongiform Encephalopathy (TSE)), therefore the source of animals, the nature and quantity of animal tissue used in manufacturing, whether there are measures employed in the manufacturing process to inactivate the infectious agents and



whether there are adequate measures to prevent cross-contamination shall be submitted to the NRA during the product evaluation and registration stage for assessment, when required by NRA. Only materials that have gone through scientific product assessment and subsequently authorized, as deemed necessary by the respective Member State, are allowed to be used for manufacturing of TM.

The manufacture of traditional medicines depends on the starting materials, manufacturing processes, building, equipment and personnel involved. It is important to recognize that quality control cannot be tested into products; i.e., quality shall be built in by design. All traditional medicines shall be manufactured under strictly controlled and monitored conditions, and shall not rely solely in finished product testing.

The purpose of these guidelines is to outline steps which shall be taken, as necessary and appropriate, by manufacturers of traditional medicines with the objective of ensuring that their products are of the intended quality and nature.



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CHAPTER 1 - QUALITY MANAGEMENT

PRINCIPLE

Traditional medicines shall be manufactured so as to ensure that they are fit for their intended use, comply with the requirements of the National Regulatory Authority (NRA) and do not place the health of the patients or consumers at risk due to inadequate safety and quality. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by the distributors. To achieve the quality objective reliably there shall be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice and thus Quality Control. It shall be fully documented and its effectiveness monitored. All parts of Quality Assurance system shall be adequately resourced with competent personnel, suitable and sufficient premises, equipment and facilities.

- 1.1. The basic concept of Quality Assurance, Good Manufacturing Practice and Quality Control are inter-related. They are described here in order to emphasise their relationships and their fundamental importance to the production and control of traditional medicines.

QUALITY ASSURANCE (QA)

- 1.2. Quality Assurance is a wide-ranging concept which covers all matters which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the object of ensuring the products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of these guidelines.

The system of Quality Assurance appropriate for the manufacture of traditional medicines shall ensure that:

- 1.2.1. traditional medicines are designed and developed in a way that takes account of the requirements of Good Manufacturing



Practice;

- 1.2.2. production and control operations are clearly specified and Good Manufacturing Practice adopted;
- 1.2.3. managerial responsibilities are clearly specified;
- 1.2.4. arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
- 1.2.5. all necessary controls on intermediate products, and any other in-process controls are carried out;
- 1.2.6. the finished product is correctly processed and checked, according to the defined procedures;
- 1.2.7. traditional medicines are not sold or supplied before a head of Quality Control / Quality Assurance has certified that each production batch has been produced and controlled in accordance with the requirements of the NRA and any other procedures relevant to the production, control and release of traditional medicines;
- 1.2.8. satisfactory arrangements exist to ensure, that the traditional medicines are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;
- 1.2.9. there is a procedure for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Quality Assurance system.
- 1.3. Good Manufacturing Practice is that part of Quality Assurance which ensures that products are consistently manufactured and controlled to the quality standards appropriate to their intended use and as required by the NRA or product specification.



Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

- 1.3.1. all manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing traditional medicines of the required quality and complying with their specifications;
- 1.3.2. critical steps of manufacturing processes and significant changes to the process are verified;
- 1.3.3. all necessary facilities for GMP are provided including:
 - 1.3.3.1. appropriate qualified and trained personnel;
 - 1.3.3.2. adequate premises and space;
 - 1.3.3.3. suitable equipment and services;
 - 1.3.3.4. correct materials, containers and labels;
 - 1.3.3.5. approved procedures and instructions;
 - 1.3.3.6. suitable storage and transportation.
- 1.3.4. instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
- 1.3.5. operators are trained to carry out procedures correctly;
- 1.3.6. records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the products as expected. Any significant deviations are fully recorded and investigated;
- 1.3.7. records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
- 1.3.8. the distribution of the products minimizes any risk to their quality;
- 1.3.9. a system is available to recall any batch of product, from sale or supply;



- 1.3.10. complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent recurrences.

QUALITY CONTROL (QC)

- 1.4. Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

The basic requirements of Quality Control are that:

- 1.4.1. adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
- 1.4.2. samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control;
- 1.4.3. test methods are either internationally accepted or other validated methods (Refer to Appendix 1: List of Internationally Accepted References for Test Methods);
- 1.4.4. records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;
- 1.4.5. the finished products contain active materials complying with the qualitative and quantitative requirements of the NRA, are of the quality required, and are enclosed within their proper containers



and correctly labelled;

- 1.4.6. records are made of the results of inspection and that testing of material, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;
- 1.4.7. no batch of product is released for sale or supply prior to certification by a head of QC / QA that it is in accordance with the requirements of the NRA;
- 1.4.8. sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

PRODUCT QUALITY REVIEW

- 1.5. Regular periodic or rolling quality reviews of all traditional medicines, including export only products, shall be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements. Such reviews shall normally be conducted and documented annually, taking into account previous reviews, and shall include at least:
 - 1.5.1. A review of starting materials and packaging materials used for the product, especially those from new sources.
 - 1.5.2. A review of critical in-process controls and finished product results.
 - 1.5.3. A review of all batches that failed to meet established specification(s) and their investigation.
 - 1.5.4. A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.



- 1.5.5. A review of all changes carried out to the processes or analytical methods.
- 1.5.6. A review of product authorization variations submitted/ granted/ refused, including those for third country (export only) dossiers.
- 1.5.7. A review of the results of the stability monitoring programme and any adverse trends.
- 1.5.8. A review of all quality-related returns, complaints and recalls and the investigations performed at the time.
- 1.5.9. A review of adequacy of any other previous product process or equipment corrective actions.
- 1.5.10. The qualification status of relevant equipment and utilities, e.g. Heating, Ventilation and Air Conditioning (HVAC), water, compressed gases, etc.
- 1.5.11. A review of Contractual Agreements to ensure that they are up to date.
- 1.5.12. A review of post-marketing commitment for new product/ variation
- 1.6. The manufacturer and manufacturing authorization holder shall evaluate the results of this review and an assessment shall be made whether corrective and preventive action shall be undertaken. Reasons for such corrective actions shall be documented. Agreed corrective and preventive actions shall be completed in a timely and effective manner. There shall be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, etc. where scientifically justified.
- 1.7. Where the product owner is not the manufacturer, there shall be a technical agreement/ contract in place between the various parties that defines their respective responsibilities in producing the quality review. The authorised person responsible for final batch certification together with the product owner shall ensure that the quality review is performed in a timely manner and is accurate.



CHAPTER 2– PERSONNEL

PRINCIPLE

There shall be an adequate number of personnel at all levels having knowledge, skill and capabilities relevant to their assigned function, and capable of handling their duties properly. They shall have the attitudes for achieving the goals of Good Manufacturing Practice (GMP).

ORGANISATION, QUALIFICATION AND RESPONSIBILITIES

- 2.1. The manufacturer shall have an organisation chart. People in responsible positions shall have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There shall be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice. The organisational structure of the company shall be such that the Production and the Quality Control Departments shall be independent of each other. Key posts shall be occupied by full-time personnel (direct supervision during operation) and shall be given full authority necessary to execute his/her duties effectively. An adequate number of trained personnel shall be available to carry out the production and the quality control operations in accordance with established procedures and specifications.
- 2.2. The head of Production Department shall be adequately trained and possess good practical experience and adequate knowledge in manufacturing traditional medicines, which can enable to perform his functions effectively.

The head of production department shall have full authority and responsibilities to manage production of products covering operations, equipment, production personnel, production area and records.

The head of the production department generally has the following responsibilities:



- 2.2.1. to ensure those products are manufactured and stored according to the appropriate documentation in order to obtain the required quality;
 - 2.2.2. to approve the instructions relating to production operations, including the in-process controls and to ensure their strict implementation;
 - 2.2.3. to ensure that the production records are evaluated and signed by a designated person before they are made available to the Quality Control Department;
 - 2.2.4. to check the maintenance of the department, premises and equipment;
 - 2.2.5. to ensure that the critical processes are appropriately verified;
 - 2.2.6. to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need;
- 2.3. The head of Quality Control Department shall have adequate training and practical experience, which can enable the person to perform the functions effectively. He/She shall be given full authority and responsibility in all quality control duties such as establishment, verification and implementation of all quality control procedures. He/She shall have the sole authority to approve starting materials, intermediates, bulk and finished products that meet the specification or to reject those which do not conform to the relevant specification or which were not manufactured in accordance with approved procedures and under the defined conditions.

The head of Quality Control shall have the following responsibilities:

- 2.3.1. to approve or reject starting materials, packaging materials and intermediate, bulk and finished products;
- 2.3.2. to evaluate batch records;
- 2.3.3. to ensure that all necessary testing is carried out;
- 2.3.4. to ensure that the critical processes are appropriately verified;
- 2.3.5. to approve sampling instructions, specification, test methods, and other quality control procedures;
- 2.3.6. to approve and monitor tests carried out under contract;
- 2.3.7. to check the maintenance of the department, premises and equipment;



- 2.3.8. to establish expiration date and shelf life specifications on the basis of stability test or available stability data related to storage conditions;
 - 2.3.9. to approve those suppliers of raw materials and packaging materials who are capable of reliably supplying products meeting the company's established quality standards;
 - 2.3.10. to evaluate all complaints received or deficiencies noted about any batch, if necessary in conjunction with other departments, and to take appropriate action accordingly;
 - 2.3.11. to maintain adequate analytical records concerning the examinations of all samples taken;
 - 2.3.12. to recommend contract-manufacturing operations which shall meet the company's specified quality standards;
 - 2.3.13. to ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.
- 2.4. The heads of Production Department and Quality Control Department shall share a joint responsibility:
- 2.4.1. to ensure that written procedures are established and to authorize written procedures and relevant document including amendments;
 - 2.4.2. to monitor and control the manufacturing environment, sanitation and hygiene;
 - 2.4.3. to verify critical processes;
 - 2.4.4. to train personnel;
 - 2.4.5. to approve and monitor the suppliers of materials and contract manufacturers;
 - 2.4.6. to establish and monitor the storage conditions for materials and products;
 - 2.4.7. to retain records;
 - 2.4.8. to monitor compliance with the requirements of Good Manufacturing Practice;
 - 2.4.9. to inspect, investigate and take samples, in order to monitor factors which may affect product quality.



TRAINING

- 2.5. All personnel shall be trained in the particular operations and in the principles of Good Manufacturing Practice.
- 2.6. Training in Good Manufacturing Practice shall be on a continuing basis and with adequate frequency to assure that employees remain familiar with Good Manufacturing Practices requirements relevant to their functions. Training in Good Manufacturing Practice shall be in accordance with written programmes approved by the head of Production Department and the head of Quality Control Department.
- 2.7. Personnel training records including Good Manufacturing Practice shall be maintained and the effectiveness of training programs shall be assessed periodically.
- 2.8. The concept of Quality Assurance and all the measures capable of improving its understanding and implementation shall be fully discussed during the training sessions.



CHAPTER 3 – PREMISES AND EQUIPMENT

PRINCIPLE

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

PREMISES

GENERAL

- 3.1. Premises for manufacturing shall be of suitable size, design, construction and location to facilitate proper operation, cleaning and maintenance.
- 3.2. Premises shall be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They shall be cleaned and, where applicable, disinfected according to detailed written procedures.
- 3.3. Steps shall be taken in order to prevent the entry of unauthorized people. Production, storage and quality control areas shall not be used as a right of way by personnel who do not work in them.
- 3.4. Lighting, temperature, humidity and ventilation shall be appropriate and such that they do not adversely affect, directly or indirectly, either the products during their manufacture and storage, or the accurate functioning of equipment.
- 3.5. Premises shall be located at a suitable site approved by the relevant authorities.
- 3.6. Premises shall be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.



- 3.7. In order to minimize the risk of a serious hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular products such as highly sensitising materials (e.g. penicillins) or biological preparations medicinal products (e.g. from live micro-organisms i.e. these products shall not be produced in the same facilities used to produce Traditional Medicines. If Traditional Medicines and Health Supplements are sharing the same manufacturing facilities cross-contamination shall be adequately addressed (examples include but not limited to: by performing cleaning verification or the use of separate equipment, etc)..
- 3.8. Premises shall be designed, constructed and maintained to protect against access and harboring of vermin, rodents, birds, insects or other animals.
- 3.9. Design shall consider prevention of mix-up between different products or their components and the possibility of cross contamination by other substances.
- 3.10. Special attention must be given for processing operations that generate dust. Measures shall be taken to prevent the generation and dissemination of dust.
- 3.11. Defined areas for the following operations are required:
- 3.11.1. Receiving and quarantine of incoming materials
 - 3.11.2. Sampling
 - 3.11.3. Storage of starting and packaging materials
 - 3.11.4. Weighing /Dispensing
 - 3.11.5. Processing
 - 3.11.6. Storage of bulk/intermediate products
 - 3.11.7. Packaging
 - 3.11.8. Equipment washing
 - 3.11.9. Storage of quarantine finished products
 - 3.11.10. Storage of approved finished products
 - 3.11.11. Designated area for quality control



Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine shall give equivalent security.

PRODUCTION AREAS

- 3.12. Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) shall be smooth, free from cracks and open joints, and shall not shed particulate matter and shall permit easy and effective cleaning and, if necessary, disinfection. The coving of junctions between walls and floors in the production areas is encouraged to facilitate cleaning.
- 3.13. Any open channels shall be avoided, but if required they shall be shallow enough to facilitate cleaning and disinfecting. All drainage shall have trapped gullies.
- 3.14. Buildings shall be effectively ventilated with air control facilities (including temperature, humidity and filtration), appropriate both to the operations undertaken within and to the external environment.
- 3.15. Production areas shall be well lit, particularly where visual on-line controls are carried out.
- 3.16. Pipework, light fittings, ventilation points and other services shall be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they shall be accessible from outside the manufacturing areas.
- 3.17. Separate areas shall be used for the production of finished products intended for external use or application and finished products intended for internal consumption solely.
- 3.18. In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions shall be taken to avoid cross-contamination and facilitate cleaning.



- 3.19. Premises for the packaging of traditional medicines shall be specifically designed and laid out so as to avoid mix-ups or cross-contamination.
- 3.20. Premises shall preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
- 3.21. Adequacy of working space, which shall allow orderly and logical placement of equipment and materials and to suit the operation, efficient flow of work, effective communication and supervision as well as to avoid crowding and disorders.
- 3.22. Changing rooms shall be directly connected to but separated from processing areas.
- 3.23. Changing rooms into the production areas shall have adequate hand washing and / or sanitizing facilities.

STORAGE AREAS

- 3.24. Storage areas shall be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected or recalled.
- 3.25. Storage areas shall be designed or adapted to ensure good storage conditions. In particular, they shall be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these shall be provided, checked and monitored.
- 3.26. Segregated and secure areas shall be provided for the storage of rejected, recalled or returned materials or products.
- 3.27. Highly active materials or products (e.g. flammable, explosive or toxic



substances) shall be stored in separate, safe and secure areas.

- 3.28. Receiving and dispatch bays shall protect materials and products from the weather. Reception areas shall be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.
- 3.29. There shall normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it shall be conducted in such a way as to prevent contamination or cross-contamination.
- 3.30. Printed packaging materials are considered critical to the conformity of the products, and special attention shall be paid to the safe and secure storage of these materials.
- 3.31. Crude (i.e. unprocessed) natural materials shall be stored in separate areas. The store area shall be well ventilated and equipped in such a way as to give protection against insects, or other animals, especially rodents. Effective measures shall be taken to prevent the spread of any such animals and microorganisms brought in with the crude natural materials to prevent fermentation, mould growth and cross-contamination. Containers shall be located in such a way as to allow free air circulation.
- 3.32. Special attention shall be paid to the cleanliness and good maintenance of the storage areas particularly when dust is generated.
- 3.33. Storage of plant materials, animal materials including parts, microorganisms, extracts, tinctures and other preparations that require special conditions of temperature, humidity or light protection; these conditions shall be provided and monitored.

QUALITY CONTROL AREAS

- 3.34. If testing is done within the premises, quality control laboratories should be separated from production areas. This is particularly important for laboratories for the handling of microorganisms.



- 3.35. Control laboratories shall be designed to suit the operations to be carried out in them. Sufficient space shall be given to avoid mix-ups and cross-contamination. There shall be adequate suitable storage space for samples and records.
- 3.36. Separate rooms may be necessary to protect sensitive instruments from vibrations, electrical interference, humidity, etc.
- 3.37. Special requirements are needed in laboratories handling particular substances such as microorganisms.

ANCILLARY AREAS

- 3.38. Rest and refreshment rooms and toilets shall be separated from other areas and shall not have direct access to controlled areas (e.g. production and storage areas).
- 3.39. Facilities for changing clothes, and for washing and toilet purposes shall be easily accessible and appropriate for the number of users.
- 3.40. Maintenance workshops shall be separated from production areas. Whenever parts and tools are stored in the production area, they shall be kept in rooms or lockers reserved for that use.
- 3.41. Animal houses shall be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

EQUIPMENT

- 3.42. Manufacturing equipment shall be designed, placed and maintained to suit its intended use.
- 3.43. Manufacturing equipment shall be installed so as to prevent contamination or minimize the risk of error and, where necessary, tested to ensure the equipment operate appropriately.



- 3.44. Manufacturing equipment shall be located at a distance from other equipment sufficient to avoid congestion and cross contamination.
- 3.45. Fixed pipework shall be clearly labelled to indicate the contents and direction of flow.
- 3.46. Balances and measuring equipment of an appropriate range and precision shall be available for production and control operation.
- 3.47. Measuring, weighing, recording and control equipment shall be calibrated and checked at defined intervals by appropriate methods. Adequate records of such activities shall be maintained.
- 3.48. Manufacturing equipment shall be designed so that it can be easily and thoroughly cleaned. It shall be cleaned according to detailed and written procedures and stored only in a clean and dry condition.
- 3.49. Dedicated equipment used to manufacture products intended for internal consumption solely shall be separated from equipment used for the manufacturing of products intended for external use or application.
- 3.50. Defective equipment shall, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.
- 3.51. Repair and maintenance operations shall not present hazard to the quality of the products. Any missing components such as nuts, springs, clips etc, shall be reported and investigated immediately.
- 3.52. Production equipment (including transfer pipes and hoses) shall not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.
- 3.53. Pipes, hoses, pumps and valves used for treated water, starting materials and the products shall be cleaned and sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.





CHAPTER 4 – SANITATION AND HYGIENE

PRINCIPLE

A high level of sanitation and hygiene shall be practised in every aspect of the manufacturing of traditional medicines.

The scope of sanitation and hygiene covers personnel, premises, equipment and utensils; in fact, anything that could become a source of contamination to the product.

All employees shall be instructed and encouraged to report to their immediate supervisor any conditions (plant, equipment or personnel) that they consider may adversely affect the quality of products.

PERSONNEL

- 4.1. All personnel, prior to employment shall undergo health examinations. During the course of their employment they shall also routinely undergo health examinations which shall include relevant examinations appropriate to the tasks that they are required to perform.
- 4.2. All personnel shall practise good personal hygiene. They shall be trained in the practices of personal hygiene. High level of personal hygiene shall be observed by all those concerned with manufacturing processes.
- 4.3. Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products shall not be allowed to handle raw materials, packaging materials, in-process materials, and finished products until the condition is improved.
- 4.4. Direct contact shall be avoided between the operator's hands and raw materials, intermediate or bulk product. Proper washing of hands and wearing of gloves shall be used if contact with hands is unavoidable.
- 4.5. To assure protection of the product from contamination as well as the safety of the personnel, appropriate protective garments shall be worn. Soiled uniforms shall be stored in closed containers until properly laundered.
- 4.6. Only authorised personnel shall be allowed to enter production areas. Visitors or untrained personnel shall, preferably, not be taken into the production and quality control areas. If this is unavoidable, they shall be



given information in advance, particularly about personal hygiene and the prescribed protective clothing. They shall be closely supervised.

- 4.7. Smoking, eating, drinking and chewing or keeping of plants, food, drink, smoking materials and personal medicines shall be restricted to specific areas and not permitted in production, laboratory, storage or other areas where they might adversely influence product quality.
- 4.8. The wearing of makeup, wrist watches and jewellery shall be prohibited in the production area however for jewellery or objects that cannot be removed; it must be covered by material that is maintained in an intact, clean and sanitary condition.

PREMISES

- 4.9. Premises used for the manufacturing of products shall be of suitable design and construction so as to facilitate good sanitation.
- 4.10. Adequate employee's washing and well ventilated toilet facilities and changing rooms shall be provided at suitable locations.
- 4.11. Suitable locker facilities shall be provided at appropriate locations for the storage of employees clothing and personal property.
- 4.12. The preparation, storage and consumption of food and beverages shall be restricted to specific areas, such as meal rooms and canteen. Facilities in such rooms must meet sanitary standards. Meal rooms and canteen rooms shall not have direct access to controlled areas (e.g. production area and areas use to store materials used for production and finished products).
- 4.13. Waste material shall not be allowed to accumulate. It shall be collected in suitable receptacles for removal to collection points outside the buildings and disposed off safely and in a sanitary manner at regular and frequent intervals.
- 4.14. Rodenticide, insecticides, fumigating agents and sanitising materials used must not contaminate equipment, raw materials, packaging materials, in-process materials or finished products. There shall be a pest control programme, documents such as layout, trending and expectations. Contract agreements shall be established, where applicable.
- 4.15. There shall be written procedures assigning responsibility for sanitation and describing cleaning schedules, methods, equipment, materials to be used and facilities to be cleaned in sufficient detail. Such written procedures shall be followed.
- 4.16. Pets are not allowed within the vicinity of the manufacturing plant.



EQUIPMENT AND UTENSILS

- 4.17. Equipment and utensils shall be cleaned both inside and outside after use according to established procedures. Cleaned equipment shall be kept or stored in a clean condition and identified with the status of cleaning, and checked for cleanliness prior to each use.
- 4.18. Vacuum or wet cleaning methods are to be preferred. Compressed air and brushes shall be used with care or avoided if possible, as they increase the risk of product contamination
- 4.19. Cleaning agents, washing and cleaning equipment shall not be a source of contamination. The choice of cleaning method and agents shall be carefully considered and justified.
- 4.20. Adequate space, preferably separated from processing areas, shall be provided for cleaning and storing mobile equipment and utensils including the storage of cleaning materials.
- 4.21. Written procedures shall be established and followed for cleaning and sanitising of equipment, utensils and containers used in the manufacture of traditional medicines.
- 4.22. These procedures shall be prepared to prevent equipment contamination by cleaning or sanitising agents and shall at least include the following:
 - 4.22.1. responsibility for cleaning,
 - 4.22.2. cleaning schedule,
 - 4.22.3. cleaning methods,
 - 4.22.4. equipment and materials used in cleaning operations,
 - 4.22.5. methods of disassembling and reassembling equipment.
 - 4.22.6. removal of previous batch identification
 - 4.22.7. protection of clean equipment and utensils from contamination prior to use
- 4.23. Records of cleaning, including the appropriate sanitising and inspection conducted prior to use shall be maintained.



CHAPTER 5 - DOCUMENTATION

PRINCIPLE

Good documentation constitutes an essential part of the quality assurance system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history of the product, from purchasing of starting materials to the distribution of finished products. It shall be able to record executed activities for maintenance, storage, quality control, distribution and other specific matters linked to GMP.

For manufacturing activities, a documentation system must be prepared. The system consisting of manufacturing formulae and instructions, specifications, procedures and records must be free from errors and clearly established.

GENERAL

- 5.1. The system of documentation shall be able to record the complete history of each batch. It shall be adequate to permit investigation and tracing of any defective products.
- 5.2. Documents shall contain all necessary information, to be kept up to date and any amendment shall be formally authorised. It shall include provision for periodic review and revision as necessary.
- 5.3. Product related records shall be retained for at least one year after the expiry date of the finished product.
- 5.4. Documents shall be designed, prepared, reviewed and distributed with care. The reproduction of working documents from master documents should not allow any error to be introduced to the reproduction process. Reproduced documents shall be clear, legible and duly authorised.
- 5.5. Documents shall be approved, signed and dated by appropriate and authorised person.
- 5.6. Documents shall have unambiguous contents; title, nature and purpose shall be clearly stated. They shall be laid out in an orderly fashion and easy



to be checked.

- 5.7. Documents shall be regularly reviewed and kept up to date. When a document has been revised, systems shall be operated to prevent inadvertent use of superseded documents.
- 5.8. Documents shall not be hand-written; although, where documents require the entry of data, these entries may be made in clear, legible, and indelible handwriting. Sufficient space shall be provided for such entries.
- 5.9. Any alteration made to the entry on a document shall be signed and dated, and where appropriate the reason of the alteration to be recorded. The alteration shall permit the reading of the original information.
- 5.10. The records shall be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture the product are traceable.
- 5.11. Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedure relating to the system in use shall be available and the accuracy of the records shall be checked and verified. If documentation is handled by electronic data processing methods, only personnel who have been authorised shall be able to enter or modify data in the computer and there shall be a record of changes and deletions; access shall be restricted by passwords or other means and the result of entry of critical data shall be independently checked and verified. Batch records electronically stored shall be protected and back-up. It is particularly important that the data are readily available throughout the period of retention.
- 5.12. The manufacturer shall practice what is documented in the written procedures. Under circumstances where there is a change in the practice, the written procedures shall be promptly updated. On the other hand, if a written procedure was revised, appropriate training shall be provided to ensure that the personnel carry out the work in accordance to the revised procedure.



QUALITY CONTROL DOCUMENTS

5.13. The following shall be readily available from the Quality Control Department:

5.13.1. Specifications

5.13.2. Sampling procedures

5.13.3. Testing procedures and records (including analytical worksheets and/or laboratory notebooks)

5.13.4. Analytical reports and/or certificates

5.13.5. Data from environmental monitoring, where appropriate.

5.13.6. Procedures for and records of the calibration of instruments and maintenance of equipment

5.14. Any Quality Control documentation relating to a batch record shall be retained for at least one year after the expiry date of the finished product.

SPECIFICATIONS

5.15. The materials used in the product shall be handled in an appropriate manner and manufactured in an appropriate controlled condition to prevent cross contamination. Documented traceability of the material and suppliers is fundamental to the quality of the finished products and shall be made available.

SPECIFICATIONS FOR NATURAL MATERIALS

5.16. The specifications for natural material shall where appropriate include the following:

5.16.1. Scientific name and if possible with reference to the authors.

5.16.2. Details to the source of the natural material (country or region of origin, and where applicable, cultivation, time of harvesting, collection procedures, possible pesticides used, etc.).

5.16.3. Whether the whole plant/animal or only a part is used.

5.16.4. When dried plant/animal is purchased, drying system shall be specified.

5.16.5. Pictorial demonstration/description of natural material, macroscopical and/or microscopical examination.

5.16.6. Storage conditions and precautions, when necessary.



5.16.7. Shelf life, where applicable

5.17. Testing procedures shall be available if the following tests are conducted, where appropriate.

5.17.1. Identification tests including, where possible, tests for known active constituents, or markers.

5.17.2. Assay, where possible, of constituents of known therapeutic activity or markers.

5.17.3. Limit tests such as ash value, and presence of essential oils and loss on drying.

5.17.4. Tests for heavy metals and for likely contaminants, foreign materials and adulterants.

5.17.5. Tests for radioactivity, mycotoxin, fungal and microbial contamination.

5.17.6. Test for residual solvents in extracts or finished products, where applicable.

5.17.7. Other tests, as required.

SPECIFICATIONS FOR STARTING MATERIALS AND PACKAGING MATERIALS

5.18. Specifications for starting materials and packaging materials shall include, if applicable. When, starting material is a natural material, please refer to paragraph 5.17.

5.18.1. a description of the materials, including:

5.18.1.1. the designated name and the internal code reference;

5.18.1.2. the reference, if any, to a pharmacopoeia monograph;

5.18.1.3. the approved suppliers and, if possible, the original producer of the products;

5.18.1.4. a specimen of printed materials;

5.18.2. directions for sampling and testing or reference to procedures;

5.18.3. qualitative and quantitative requirements with acceptance limits;

5.18.4. storage conditions and precautions;



5.18.5. the maximum period of storage before re-examination

SPECIFICATIONS FOR INTERMEDIATE AND BULK PRODUCTS

5.19. Specifications for intermediate and bulk products shall be available if these are purchased or transferred, or if data obtained from intermediate products are used for the evaluation of the finished product. The specifications shall be similar to specifications for starting materials or for finished products, as appropriate.

SPECIFICATIONS FOR FINISHED PRODUCTS

5.20. The specifications for finished product where appropriate shall include the following tests:

5.20.1. Microbial limits;

5.20.2. Heavy metals limits;

5.20.3. Uniformity of weight (for tablets and capsules), disintegration (for tablets, capsules and pills), hardness and friability (for tablets), and viscosity (for internal and external liquids);

5.20.4. Physical appearance such as colour, taste, texture, size, etc.

5.20.5. Other tests, as required

5.21. The specifications shall also include:

5.21.1. The designated name of the product and the internal code reference where applicable;

5.21.2. The formula or a reference to;

5.21.3. A description of the dosage form and package details;

5.21.4. Directions for sampling and testing or a reference to procedures, where applicable;

5.21.5. The qualitative and quantitative requirements, with the acceptance limits, where applicable;

5.21.6. The storage condition and any special handling precautions, where applicable;

5.21.7. The shelf life

PRODUCTION DOCUMENTS



MANUFACTURING FORMULA AND PROCESSING INSTRUCTIONS

Formally authorised Manufacturing Formula and Processing Instructions shall exist for each product and batch size to be manufactured. They are often combined in one document.

5.22. The Manufacturing Formula shall include:

- 5.22.1. The name of the product, with a product reference code relating to its specification;
- 5.22.2. A description of the product dosage form, strength of the product and batch size;
- 5.22.3. A list of all starting materials to be used, with the amount of each, described using the designated name and a reference which is unique to that material; mention shall be made of any substance that may disappear in the course of processing;
- 5.22.4. A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

5.23. The Processing Instructions shall include:

- 5.23.1. A statement of the processing location and the principal equipment to be used;
- 5.23.2. The methods, or reference to the methods, to be used for setting up the equipment (e.g. Cleaning, assembling, calibrating);
- 5.23.3. Detailed stepwise processing instruction (e.g. Checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures);
- 5.23.4. The instructions for any in-process controls with their limits;
- 5.23.5. Where necessary, the requirements for bulk storage of the products; including the container, labelling and special storage conditions where applicable;
- 5.23.6. Any special precautions to be observed.

5.24. The processing instructions shall describe the different operations carried out upon the crude material such as sorting, cleaning, drying, crushing and sifting, and include drying time and temperatures, and methods used to control fragment or particle size. It shall also describe the sieving process or other methods of removing foreign materials.



- 5.25. In particular, there shall be written instructions and records, which ensure that each container of the product is carefully examined to detect any adulteration/substitution or presence of foreign matter, such as metal or glass pieces, animal parts or excrement, stones, sand, etc., or rot and signs of decay.
- 5.26. For product preparation, instructions shall include details of base or solvent, time and temperatures of extraction, details of any concentration stages and methods used.

PACKAGING INSTRUCTIONS

- 5.27. There shall be formally authorised Packaging Instructions for each product, pack size and type. These shall normally include, or have a reference to the following:
- 5.27.1. Name of the product;
 - 5.27.2. Description of its product dosage form, and strength where applicable;
 - 5.27.3. The pack size expressed in terms of the number, weight or volume of the product in the final container;
 - 5.27.4. A complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
 - 5.27.5. Where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;
 - 5.27.6. Special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
 - 5.27.7. A description of the packaging operation, including any significant additional operations, and equipment to be used;
 - 5.27.8. Details of in-process controls with instructions for sampling and acceptance limits.

BATCH PROCESSING RECORDS

- 5.28. Batch Processing Record is that part of Batch Manufacturing Record and shall be kept for each batch processed. It shall be based on the relevant parts of the currently approved Manufacturing Formula and Processing



Instructions. The method of preparation of such records shall be designed to avoid transcription errors. The record shall carry the batch number of the product being manufactured.

- 5.29. Before any processing begins, there shall be recorded verification that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use.
- 5.30. During processing, the following information shall be recorded at the time each action is taken and, after completion, the record shall be dated and signed in agreement by the person responsible for the processing operations:
- 5.30.1. The name of the product;
 - 5.30.2. Dates and times of initiation, of significant intermediate stages and of completion of production;
 - 5.30.3. Name of the person responsible for each stage of production;
 - 5.30.4. Date and the signature of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. Weighing);
 - 5.30.5. The batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed materials added);
 - 5.30.6. Any relevant processing operation or event and major equipment used;
 - 5.30.7. A record of the in-process controls and the date and signature of the person(s) carrying them out, and the results obtained;
 - 5.30.8. The product yield obtained at different and pertinent stages of manufacture;
 - 5.30.9. Notes on special problems including details, with signed authorisation for any deviation from the manufacturing formula and processing instructions.

BATCH PACKAGING RECORDS

- 5.31. A Batch Packaging Record is part of Manufacturing Record and shall be kept for each batch or part of batch processed. It shall be based on the relevant parts of the Packaging Instructions and the method of preparation of such records shall be designed to avoid transcription errors. The record



shall carry the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained.

- 5.32. Before any packaging operation begins, there shall be recorded checks that the equipment and work station are clear of previous products, documents, or materials not required for the planned packaging operations, and that equipment is clean and suitable for use.
- 5.33. The following information shall be entered at the time each action is taken and, after completion, the record shall be dated and signed in agreement by the person(s) responsible for the packaging operations:
- 5.33.1. The name of the product;
 - 5.33.2. The date(s) and times of the packaging operations; when there is the risk of contamination, the packaging activity shall be done within the day itself
 - 5.33.3. The name of the responsible persons carrying out the packaging operation;
 - 5.33.4. The date and signature of the operators of the different significant steps;
 - 5.33.5. Records of verification for identity and conformity with the packaging instructions including the results of in-process controls;
 - 5.33.6. Details of the packaging operations carried out, including references to equipment and the packaging lines used;
 - 5.33.7. Whenever possible, samples of printed packaging materials used, which include the batch/lot number, expiry date and any additional overprinting;
 - 5.33.8. Notes on any special problems or unusual events including details, with date and signed authorisation from the manufacturing formula and processing instructions;
 - 5.33.9. The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation.

STANDARD OPERATING PROCEDURES (SOPs) AND RECORDS

- 5.34. There shall be written procedures and records for the receipt of each delivery of each starting materials and packaging material.



The records of the receipts shall include:

- 5.34.1. The name of material on the delivery note and the containers;
 - 5.34.2. The “ in-house” name and/or code of material (if different from 5.29.1);
 - 5.34.3. Date of receipt, date and signature of the receiving staff
 - 5.34.4. Supplier's name and manufacturer's name;
 - 5.34.5. Manufacturer's batch or reference number;
 - 5.34.6. Total quantity and number of containers received;
 - 5.34.7. The batch number assigned after receipt;
 - 5.34.8. Any relevant comment (e.g. State of the containers).
- 5.35. There shall be written procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.
- 5.36. Standard operating procedures shall be available for the operation of each equipment and placed in close proximity to the instrument or equipment.
- 5.37. There shall be standard operating procedures for sampling, which specify the person(s) authorised to take samples, sampling tools and the sampling instructions.
- 5.38. There shall be a standard operating procedure describing the details of the batch / lot numbering system, with the objective of ensuring that each batch of intermediate, bulk, or finished product is identified with a specific batch number. The batch numbering procedures shall assure that the same batch numbers will not be repeatedly used; this applies also to reprocessing.
- 5.39. Batch number allocation shall be immediately recorded, e.g. in a logbook. The record shall include date of allocation, product identity, and size of batch.
- 5.40. The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage shall be related to each other.
- 5.41. Written procedure for quarantine, release and rejection shall be available for materials and products, and in particular for the release for sale of the finished product by the authorised person.
- 5.42. Records shall be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.



- 5.43. Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached shall be available for:
- 5.43.1. equipment assembly;
 - 5.43.2. operation of analytical apparatus and calibration;
 - 5.43.3. maintenance, cleaning, and sanitisation of equipment and premises;
 - 5.43.4. personnel matters including qualification, GMP training, clothing, and hygiene;
 - 5.43.5. environmental monitoring;
 - 5.43.6. pest control;
 - 5.43.7. adverse product reactions, complaints and product recalls
 - 5.43.8. returns and recovered products, rejected products/materials;
 - 5.43.9. disposal and destruction of the rejected products/materials;
 - 5.43.10. self-inspection / quality audit
- 5.44. Logbooks shall be kept for major or critical equipment and shall record, as appropriate, any calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.
- 5.45. Logbooks shall be recorded in chronological order for the use of all equipment and the areas where the products have been processed.
- 5.46. Several of the above-mentioned procedures, specifications and/or records may be combined together in one specific document.



CHAPTER 6 - PRODUCTION

PRINCIPLE

With the premises and equipment provided, the processes used in production shall be capable of yielding finished products which conform to their specifications. Defined manufacturing procedures are necessary to ensure that production, quality control and other relevant personnel are instructed on the details of the processes concerned.

GENERAL

- 6.1. Production shall be performed and supervised by competent people.
- 6.2. All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution shall be done in accordance with written procedures or instructions and, where necessary, recorded.
- 6.3. All incoming materials shall be checked to ensure that the consignment corresponds to the order. Containers shall be cleaned where necessary and labelled with the prescribed data.
- 6.4. Damage to containers and any other problem, which might adversely affect the quality of a material, shall be investigated, recorded and reported to the Quality Control Department.
- 6.5. Incoming materials and finished products shall be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.
- 6.6. Intermediate and bulk products purchased as such shall be handled on receipt as though they were starting materials.
- 6.7. All materials and products shall be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch



segregation and stock rotation.

- 6.8. Checks on yields, and reconciliation of quantities, shall be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
- 6.9. Operations on different products shall not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.
- 6.10. At every stage of processing, products and materials shall be protected from microbial and other contamination. Any treatment used to reduce fungal/microbial contamination or other infestation shall be documented.
- 6.11. When working with dry materials and products, special precautions shall be taken to prevent the generation and dissemination of dust.
- 6.12. At all times during processing, all materials, bulk containers, major items of equipment and where appropriate, rooms used shall be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication shall also mention the stage of production.
- 6.13. Labels applied to containers, equipment or premises shall be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example, quarantined, accepted, rejected, clean, etc.).
- 6.14. Checks shall be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.
- 6.15. Access to production premises shall be restricted to authorised personnel.
- 6.16. Water used as ingredients or for final rinsing of production equipment shall be treated to minimise microbial contamination.



VERIFICATION

- 6.17. Verification work that is needed to prove control of critical aspects of particular operations shall be identified and documented. Significant changes to the facilities, equipment, testing and the processes which may affect the quality of the product shall be verified. A risk assessment approach shall be used to determine the scope and extent of verification.

Please refer to details in Appendix 2 – Verification.

PREVENTION OF CROSS-CONTAMINATION IN PRODUCTION

- 6.18. Contamination of a starting material or of a product by another material or product shall be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated.
- 6.19. Cross-contamination shall be avoided by appropriate technical or organisational measures, for example:
- 6.19.1. Production in segregated area, or by campaign (separation in time) followed by appropriate cleaning;
 - 6.19.2. Providing appropriate air-locks and air extraction;
 - 6.19.3. Minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
 - 6.19.4. Wearing protective clothing inside areas where products with special risk of cross-contamination are processed;
 - 6.19.5. Using the approved cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
 - 6.19.6. Using "closed systems" of production;
 - 6.19.7. Testing for residues and use of cleaning status labels on equipment.
 - 6.19.8. Specific provisions for sampling, weighing, mixing and processing operations of crude plants whenever dust is generated.
- 6.20. Measures to prevent cross-contamination and their effectiveness shall be checked periodically according to set procedures.



STARTING MATERIALS

- 6.21. The purchase of starting materials is an important operation which shall involve personnel who have a particular and thorough knowledge of the suppliers.
- 6.22. Starting materials shall only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials are discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements, as well as complaints and rejection procedures are discussed with the manufacturer and the supplier. The supplier of the materials shall be adequately assessed and the assessment shall be recorded.
The supplier assessment programme shall include the establishment of an approved supplier list which may include alternative supplier, initial assessment before placing the supplier on the approved supplier list and periodic assessment thereafter, provision for on-site audit of the supplier premises, etc.
- 6.23. For each delivery, the containers shall be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.
- 6.24. If one material delivery is made up of different batches, each batch shall be considered as separate for sampling, testing and release.
- 6.25. Starting materials in the storage areas shall be appropriately labelled. Labels shall bear at least the following information:
- 6.25.1. The designated name of the product and the internal code reference where applicable
 - 6.25.2. A batch number given at receipt
 - 6.25.3. Where appropriate, the status of the contents (e.g. In quarantine, on test, released, rejected)
- 6.26. There shall be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn shall be identified.
- 6.27. Only starting materials which have been released by the Quality Control Department and which are within their shelf life shall be used.



- 6.28. Starting materials shall only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.
- 6.29. Each dispensed material and its weight or volume shall be independently checked and the check recorded.
- 6.30. Materials dispensed for each batch shall be kept together and conspicuously labelled as such.

PROCESSING OPERATIONS: INTERMEDIATE AND BULK PRODUCTS

- 6.31. Before the introduction of a Master Formula it shall be evaluated sufficiently to determine that it is suitable for routine processing operations, and the ability of the process to be reproducible.
- 6.32. Production personnel shall follow defined and authorised procedures for every stage of each manufacturing process.
- 6.33. Any deviation from defined procedures shall be recorded and agreed upon between the head of Production Department and the head of Quality Control Department.
- 6.34. Before any manufacturing begins, steps shall be taken to ensure that the work area and equipment are free from any materials, products, or documents, not required for the current operation.
- 6.35. Any necessary in-process controls and environmental controls shall be carried out and recorded.
- 6.36. Before applying labels or marks to materials and equipment, all irrelevant labels or marks previously used shall be removed.
- 6.37. The final yield of each production stage shall be recorded and checked against the theoretical yield range. Any significant deviation from the expected yield shall be recorded and investigated..
- 6.38. Storage of materials and bulk products must be under controlled condition.



PACKAGING MATERIALS

- 6.39. The purchase, handling and control of primary and printed packaging material shall be accorded attention similar to that given to starting materials.
- 6.40. Particular attention shall be paid to printed materials. They shall be stored in adequately secure condition such as to exclude unauthorised access. Cut labels and other loose printed materials shall be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials shall be issued for use only by authorised personnel following an approved and documented procedure.
- 6.41. Each delivery or batch of printed or primary packaging material shall be given a specific reference number or identification mark.
- 6.42. Outdated or obsolete primary packaging material or printed packaging material shall be destroyed and this disposal recorded.

PACKAGING OPERATIONS

- 6.43. When setting up a programme for the packaging operations, particular attention shall be given to minimising the risk of the cross-contamination, mix-ups or substitutions. Different products shall not be packaged in close proximity unless there is physical segregation.
- 6.44. Before packaging operations, steps shall be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance shall be performed according to an appropriate checklist.
- 6.45. The name and batch number of the product being handled shall be displayed at each packaging station or line.
- 6.46. All products and packaging materials to be used shall be checked on delivery to the packaging department for quantity, identity and conformity



with the Packaging Instructions.

- 6.47. Containers for filling shall be clean before filling. Measures shall be taken to prevent any contaminants such as glass fragments and metal particles.
- 6.48. Normally, filling and sealing shall be followed as quickly as possible by labelling. If it is not the case, appropriate procedure shall be applied to ensure that no mix-ups or mislabelling could occur.
- 6.49. The correct performance of any printing operation (for example batch/lot numbers, expiry dates) to be done separately or in the course of the packaging shall be checked and recorded. Attention shall be paid to printing by hand which shall be re-checked at regular intervals.
- 6.50. Special care shall be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.
- 6.51. Checks shall be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.
- 6.52. Printed and embossed information on packaging materials shall be distinct and resistant to fading or erasing.
- 6.53. On-line control of the product during packaging shall include at least checking the following:
 - 6.53.1. General appearance of the packages;
 - 6.53.2. Whether the packages are complete;
 - 6.53.3. Whether the correct products and packaging materials are used;
 - 6.53.4. Whether any over-printing is correct;
 - 6.53.5. Correct functioning of line monitors.
- 6.54. Samples taken away from the packaging line shall not be returned.
- 6.55. Products which have been involved in an unusual event shall only be reintroduced into the process after special inspection, investigation and



approval by authorised personnel. Detailed record shall be kept of this operation.

- 6.56. Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced shall be investigated and satisfactorily accounted for before release.
- 6.57. Upon completion of a packaging operation, any unused batch-coded packaging materials shall be destroyed and the destruction recorded. A documented procedure shall be followed if uncoded printed materials are returned to stock.

FINISHED PRODUCTS

- 6.58. Finished products shall be held in quarantine until their final release under conditions established by the manufacturer.
- 6.59. The evaluation of finished products and documentation which is necessary before release of product for sale is described in Chapter 7 (Quality Control).
- 6.60. After release, finished products shall be stored as usable stock under conditions established by the manufacturer.

REJECTED, RECOVERED AND RETURNED MATERIALS

- 6.61. Rejected materials and products shall be clearly marked as such and stored separately in restricted areas. They shall either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken shall be approved and recorded by authorised personnel.
- 6.62. The reprocessing of rejected products shall be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Record shall be kept of the reprocessing.
- 6.63. The recovery of all or part of earlier batches which conform to the required



quality by incorporation into a batch of the same product at the defined stage of manufacture shall be authorised beforehand. This recovery shall be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery shall be recorded.

- 6.64. The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, shall be considered by the Quality Control Department.
- 6.65. Products returned from the market and which have left the control of the manufacturer shall be destroyed unless without doubt their quality is satisfactory; they may be considered for re-sale, re-labelling or recovery in 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 it requires, its condition and history, and the time elapsed since it was issued shall all be taken into account in this assessment. Where any doubt arises over the quality of the product, it shall not be considered suitable for re-issue or re-use, although basic chemical reprocessing to recover active ingredient may be possible. Any action taken shall be appropriately recorded.



CHAPTER 7 – QUALITY CONTROL

PRINCIPLE

Every manufacturing establishment shall have a quality control system so designed as to ensure that the product are manufactured in accordance with adequate conditions and procedures and continue to meet the established specifications.

Quality control is not confined to laboratory operations, but must involve all decisions which may concern the quality of the product.

For this purpose there shall be an appropriate and independent Quality Control Department.

GENERAL

- 7.1. Quality control is concerned with sampling, specifications, testing, organisation, documentation and release procedures which ensure that the necessary tests are in fact carried out, and that the materials are not released for use, nor products released for sale and supply until their quality has been assessed to be satisfactory.
- 7.2. The Quality Control Department shall have a designated area with sufficient and well trained staff to perform any required analysis before, during and after manufacture.
- 7.3. If the in-house Quality Control Department cannot perform certain specific analysis, the services of accredited/ recognised external laboratory can be used to conduct the tests.
- 7.4. Finished products assessment shall embrace all relevant factors, including production condition, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of final finished pack.



- 7.5. Quality Control personnel shall have access to production areas for sampling and investigation as appropriate.
- 7.6. Quality Control personnel shall have particular expertise in products in order to be able to carry out identification tests and recognise adulteration, the presence of fungal growth, infestations, and non-uniformity when receiving and checking crude materials.
- 7.7. The identity and quality of materials and finished products shall be checked / tested. The presence of individual ingredient in pre-mixes shall be confirmed.
- 7.8. Besides these principal duties, the Quality Control Department as a whole will also have other duties, such as to establish and implement all quality control procedures, keep the reference samples of materials and products, ensure the correct labelling of containers of materials and products, ensure the monitoring of the stability of the products, etc. All these operations shall be carried out in accordance with written procedures and recorded.
- 7.9. The stability of the finished product shall be monitored according to a continuous appropriate programme that will permit the detection of any stability issue associated with the formulation in the marketed package.

SAMPLING

- 7.10. Due to the fact that crude material shall be an aggregate of individual natural materials i.e. contain an element of heterogeneity, the sampling has to be carried out with special care by competent personnel. Each batch shall be identified by its own documentation.
- 7.11. The sample taking shall be done in accordance with approved written procedures that describe:
 - 7.11.1. the method of sampling
 - 7.11.2. the equipment to be used
 - 7.11.3. the amount of the sample to be taken



- 7.11.4. instructions for any required subdivision of the sample
 - 7.11.5. the type and condition of the sample container to be used
 - 7.11.6. the identification of containers sampled
 - 7.11.7. the storage conditions
 - 7.11.8. instructions for the cleaning and the storage of sampling equipment.
- 7.12. Reference samples shall be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process. (e.g. beginning or end of a process).
- 7.13. Sample containers shall bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn.
- 7.14. Reference samples from each batch of finished products shall be retained till one year after the expiry date. Finished products shall usually be kept in their final packaging and stored under the recommended conditions. Samples of starting materials (other than solvents, gases and water) shall be retained for at least two years after the release of the product if their stability allows. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter. Reference samples of materials and products shall be of a size sufficient to permit at least a full re-examination.

TESTING

- 7.15. All testing operations described in the marketing authorization shall be carried out according to approved methods which shall be internationally accepted (Refer to Appendix 1: List of Internationally Accepted References for Test Methods) or other validated test methods.
- 7.16. The results obtained shall be recorded and verified to make sure that they are consistent with each other. Any calculations shall be critically examined.
- 7.17. The test performed shall be recorded and the records shall include at least



the following data:

- 7.17.1. Name of the material or product and, where applicable, dosage form
 - 7.17.2. Batch number and, where appropriate, the manufacturers and/or supplier
 - 7.17.3. References to the relevant specifications and testing procedures
 - 7.17.4. Test results, including observations and calculations, and reference to any certificates of analysis
 - 7.17.5. Dates of testing, the name of the analyst and the name of the external laboratory, if applicable
 - 7.17.6. Date and signature of the persons who performed the testing
 - 7.17.7. Date and signature of the persons who verified the testing and the calculations, where appropriate
 - 7.17.8. A clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person
- 7.18. All the in-process controls, including those made in the production area by production personnel, shall be performed according to methods approved by Quality Control and the results recorded.
- 7.19. Special attention shall be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media. They shall be prepared in accordance with written procedures and recorded.
- 7.20. Laboratory reagents intended for prolonged use shall be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media shall be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardisation and the last current factor shall be indicated.
- 7.21. For some kinds of data (e.g. analytical test results, yields, environmental controls) it is recommended that records in a manner permitting trend evaluation be kept.



- 7.22. In addition to the information which is part of the batch record, other original data such as laboratory notebooks and/or reports shall be retained and readily available.

ON GOING STABILITY PROGRAMME

- 7.23. After marketing, the stability of the product shall be monitored according to a continuous appropriate programme that will permit the detection of any stability issue associated with the formulation in the marketed package.
- 7.24. The purpose of the on-going stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.
- 7.25. This mainly applies to the product in the package in which it is marketed / sold, but consideration shall also be given to the inclusion in the programme of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product shall be evaluated and studied under ambient conditions. In addition, consideration shall be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.
- 7.26. The on-going stability programme shall be described in a written protocol and results formalised as a report. The equipment used for the on-going stability programme (stability chambers among others) shall be qualified and appropriately maintained.
- 7.27. The protocol for an on-going stability programme shall extend to the end of the shelf life period and shall include, but not be limited to, the following parameters:



- 7.27.1. Number of batch(es) per strength and different batch sizes, where applicable
 - 7.27.2. Relevant physical, chemical, microbiological and biological test methods, stability indicating parameters, where applicable
 - 7.27.3. Acceptance criteria
 - 7.27.4. Reference to test methods
 - 7.27.5. Description of the container closure system(s)
 - 7.27.6. Testing intervals (time points)
 - 7.27.7. Description of the conditions of storage
 - 7.27.8. Other applicable parameters specific to the finished product
- 7.28. The protocol for the on-going stability program can be different from that of the initial long-term stability study as submitted in the marketing authorization dossier provided that this is justified and documented in the protocol.
- 7.29. The number of batches and frequency of testing shall provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, shall be included in the stability program (unless none are produced during that year). Scientific justification has to be provided in the event that the principle of bracketing and matrixing designs is applied.
- 7.30. In certain situations, additional batches shall be included in the on-going stability program. For example, an on-going stability study shall be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation shall also be considered for inclusion.
- 7.31. Results of on-going stability studies shall be made available to key personnel and, in particular, to the Authorised Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there shall be a written agreement between the parties concerned. Results of on-going stability studies shall be



available at the site of manufacture for review by the competent authority.

- 7.32. Out of specification or significant atypical trends shall be investigated. Any confirmed out of specification result, or significant negative trend, shall be reported to the relevant competent authorities. The possible impact on batches on the market shall be considered in accordance with Chapter 9 – Complaints and Product Recalls of this GMP Guide and in consultation with the relevant competent authorities.
- 7.33. A summary of all the data generated, including any interim conclusions on the programme, shall be written and maintained. This summary shall be subjected to periodic review.
- 7.34. For stability study requirements, reference shall be made to the ASEAN Guidelines on Stability Study and Shelf Life of Traditional Medicine.



CHAPTER 8 – CONTRACT MANUFACTURE AND ANALYSIS

PRINCIPLE

Contract manufacture and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or work of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties and responsibilities of each party. The contract must clearly state the way in which the authorized person releasing each batch of product for sale exercises his full responsibility.

CONTRACT MANUFACTURE

- 8.1. Contract manufacture shall have a written contract agreement between the contract giver and the Contract Acceptor, which clearly establishes the duties and responsibilities of each party. All arrangements for contract manufacture, including any proposed changes in technical or other arrangements, shall be in accordance with the NRA requirements for the product concerned.

CONTRACT ANALYSIS

- 8.2. Contract analysis must have a written contract agreement between the contract giver and the Contract Acceptor which clearly establishes the duties and responsibilities of each party.
- 8.3. All arrangements for contract analysis, including any proposed changes in technical or other arrangements, shall be in accordance with NRA's requirements for the product concerned.

THE CONTRACT GIVER

- 8.4. The Contract Giver shall be responsible for assessing the competency of the Contract Acceptor in successfully carrying out the work/test required and



for ensuring by means of the contract that the principles of GMP described in these guidelines are followed.

- 8.5. The Contract Giver shall provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the NRA requirements. The Contract Giver shall ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.
- 8.6. The Contract Giver shall ensure that all products and materials delivered by the Contract Acceptor comply with their specifications.

THE CONTRACT ACCEPTOR

- 8.7. The Contract Acceptor has adequate premises, equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the Contract Giver. Contract manufacture shall be undertaken only by a manufacturer who is the holder of a manufacturing authorization issued by the NRA.
- 8.8. The Contract Acceptor shall ensure that all products or materials received are suitable for their intended purpose.
- 8.9. The Contract Acceptor shall not pass to a third party any of the work entrusted to him under the contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party shall ensure that the manufacturing and the analytical information is made available in the same way as between the original Contract Giver and Contract Acceptor.
- 8.10. The Contract Acceptor shall refrain from any activity that may adversely affect the quality of the product manufactured/tested for the contract giver.



THE CONTRACT

- 8.11. A contract shall be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities relating to the manufacture and the control of the product. Technical aspects of the contract shall be drawn up by competent persons suitably knowledgeable in traditional medicines manufacturing, analysis and Good Manufacturing Practice. All arrangement for manufacture and analysis must be in accordance with the NRA requirement and agreed by both parties.
- 8.12. The contract shall specify the way in which the head of Quality Control Department releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of the NRAs.
- 8.13. The contract shall describe clearly who is responsible for purchasing materials, testing and releasing materials, undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In case of contract analysis, the contract shall state whether or not the Contract Acceptor shall take samples at the premises of the manufacturer.
- 8.14. Manufacturing, analytical and distribution records, and reference samples shall be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect / recall procedures of the Contract Giver.
- 8.15. The contract shall permit the Contract Giver to visit the facilities of the Contract Acceptor.
- 8.16. In the case of contract analysis, the Contract Acceptor shall understand that he is subject to inspection by the competent Authorities.



CHAPTER 9 – COMPLAINTS AND PRODUCT RECALLS

PRINCIPLE

All complaints and other information concerning potentially defective products must be kept and reviewed according to written procedures. In order to provide for all contingencies, a system shall be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

PRODUCT COMPLAINTS

- 9.1. Product complaints are usually concerned with the quality of the product such as its physical properties, or condition of its packaging. Complaints (internal or external) could be made to the manufacturer, verbally or in writing by consumers, distributors or the NRA.
- 9.2. All complaints shall be investigated and evaluated. Written procedures describing the handling of all written and verbal complaints regarding the product shall be established and followed. Such procedures shall include provisions for review by the Quality Control unit. A written record of each complaint shall be maintained in a file designated for product complaints.
- 9.3. A person shall be designated responsible for handling the complaints.
- 9.4. There shall 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.
- 9.5. Any complaint concerning a product defect shall be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control shall be part of the team.
- 9.6. Special attention shall be given in establishing whether the product which is the subject of a complaint, genuine or is a counterfeit product.



- 9.7. If a product defect is discovered or suspected in a batch, consideration shall be given to check other batches in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch shall be investigated.
- 9.8. All decisions and measures taken as a result of a complaint shall be recorded and referenced to the corresponding batch records.
- 9.9. Complaint records shall be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.
- 9.10. For recurring problem, a trending shall be established in order to identify the possible systemic defects.
- 9.11. The NRA shall be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, or any other serious quality problems with a product.
- 9.12. The NRA and the complainant shall be furnished with a summary of the action taken.

PRODUCT RECALLS

- 9.13. Responsibility and procedures for recall of the product shall be established by the manufacturer to facilitate the recall of a batch from any link of the distribution chain when this becomes necessary.
- 9.14. The recall procedures shall take into account the degree and level of recall which in line with the NRA requirement.
- 9.15. Any action taken to recall a product suspected or known to be defective or hazardous, shall be done immediately and in accordance with a pre-determined plan. The procedures to be followed shall be specified in writing and made known to all that may be concerned.



- 9.16. A person shall be designated as responsible for execution and co-ordination of recalls and shall be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person shall normally be independent of the sales and NRA requirements.
- 9.17. There shall be established written procedures, regularly checked and updated when necessary, in order to organise any recall activity.
- 9.18. Recall operation shall be capable of being initiated immediately and at any time.
- 9.19. All NRA of all countries to which products may have been distributed shall be informed immediately if products are intended to be recalled because they are, or are suspected of being defective.
- 9.20. The distribution records shall be readily available to the person(s) responsible for recalls, and shall contain sufficient information on distributor / importer / retailer / wholesalers and directly supplied customers (with latest and valid addresses, contact number including mobile phone, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products.
- 9.21. Recalled products shall be identified, recorded and stored separately in a secure area while awaiting a decision on their fate.
- 9.22. The progress of the recall process shall be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of the products.
- 9.23. The effectiveness of the arrangements for recalls shall be evaluated regularly.

COMPLAINTS ON ADVERSE PRODUCT REACTIONS



- 9.24. Unexpected adverse product reactions resulting from the use of the product must be thoroughly investigated and documented. Reports of serious unexpected adverse reactions shall be immediately forwarded to the NRA.



CHAPTER 10 – SELF-INSPECTION

PRINCIPLE

Self-inspections shall be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures.

- 10.1. Personnel matters, premises, equipment, documentation, production, quality control, distribution of the products, arrangements for dealing with complaints and recalls, and self-inspection, shall be examined at intervals following a pre-arranged program in order to verify their conformity with the principles of Quality Assurance.
- 10.2. Self-inspection shall be conducted in an independent and detailed way by designated competent person(s) from the company. The independent audits by external experts may also be useful.
- 10.3. All self-inspections shall be recorded. Reports shall contain all the observations made during the inspections and, where applicable, proposals for corrective actions and preventive actions, and corresponding time frames. Statements on the actions subsequently taken shall also be recorded.



GLOSSARY

The following definitions are adopted and used for the purpose of these guidelines and shall not be taken as legislative definitions:

Authorised Person

A person who is formally and properly empowered and has the authority to perform specified duties associated with the company.

Adverse Product Reactions

Adverse product reaction is an allergic or any other untoward reaction, toxic reaction, fatal or near fatal reaction etc., which are unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of a disease.

Batch (or Lot)

A quantity of any traditional medicine produced during a given cycle of manufacture and from a specific formulation order, that is uniform in character and quality [the essence of a manufacturing batch is its homogeneity].

Batch Number

A designation [in numbers, or letters, or combination of both] that identifies the batch and that permits the complete history of the batch including all stages of production, control and distribution, to be traced and reviewed.

Bracketing

It is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all time points as in a full design.)

Bulk Product

Any product that has completed all processing stages up to, but not including, final packaging.

Critical Steps/Process

A step/process which can manifest as a gain/loss of specific activity and/or an increase/decrease in an impurity level or whether the operating point is near the



edge of failure and how well this can be controlled which can affect safety, purity or efficacy of a product.

Crude

Existing in a natural state and unprocessed form.

Date of Manufacture

A date fixed for the individual batch, indicating the starting date of the manufacture.

Designated Name

A name assigned to specific material or item to distinguish one from another.

Documentation

All written procedures, instructions and records involved in the manufacture of a traditional medicine.

Expiry Date

A date fixed for each individual batch before which the batch still meets the required standard specifications for quality.

Finished Product

A traditional medicine which has undergone all the stages of manufacture.

In-Process Control

Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate Product

Any material or mixture of materials which have to undergo one or more stages of processing to become a bulk product.

Markers

Constituents of a natural material, which is chemically defined, and of interest for control purposes.

Marketing Authorization

An official document issued by the competent National Regulatory Authority (NRA) for the purpose of marketing or free distribution of a product after evaluation.



Material

Any substance or component with certain physical properties that are used as components in production or manufacturing.

Matrixing

It is a design in the conduct of stability studies in such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point.

Natural Materials

Comminuted or powdered natural materials, extracts, tinctures, fatty or essential oils, resins, gums, balsams, expressed juices, etc. prepared from plant, animal or mineral, and preparations whose production involves a fractionation, purification or concentration process, excluding chemically defined isolated constituents. A natural ingredient can be regarded as the active ingredient whether or not the constituents with therapeutic activities are known.

National Regulatory Authority (NRA)

It is the country regulatory authority or part of that Member State which exercises a legal right to control the import, manufacture, export, distribution, transfer, use and the sale of traditional medicines (TM) within that member state jurisdiction and which may take regulatory action to ensure that the TM products marketed within its jurisdiction comply with regulatory requirement.

Packaging

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

Packaging Materials

Any material, including printed material, employed in the packaging of a traditional medicine, such as containers, closures, bags, packing, label materials [labels, inserts, etc.], seals, binding materials, adhesives and tapes.

Product Recall

It is an action taken to remove a product from the market. Recalls maybe initiated by the National Regulatory Authority (NRA) or a voluntary action on the part of manufacturer and distributor to carry out their responsibility to protect the public health and well-being from products that present a risk of injury or gross deception or are otherwise deceptive.

Qualification



Action approving and documenting the equipment or ancillary systems are properly installed, work correctly and actually lead to expected results.

Quarantine

The status of starting materials, intermediate, bulk and finished products set apart [physically or by system] while awaiting a decision on their suitability for processing, packaging or distribution.

Raw Materials

All materials whether active or inactive that are employed in the processing of traditional medicines.

Reference sample

A sample representing the batch of starting/packaging materials or intermediate/finished products from which they are taken, stored for the purpose of being analyzed shall the need arise during the shelf life of the batch concerned.

Rejected

The status of starting materials, intermediate, bulk or finished products which are not permitted to be used for processing, packaging or distribution and shall be discarded in a safe manner.

Released or Passed

The status of starting materials, intermediate, bulk or finished products which are allowed to be used for processing, packaging or distribution.

Reprocessing

A method of repeating the process of all or part of a batch with an unacceptable quality to undergo special or additional processing before release.

Sanitation

Hygienic control on manufacturing processes, including personnel, premises, equipment and handling of materials [from starting materials to finished products].

Starting Materials

Any substance or mixture of substances (pre-mix) used in the production of a traditional medicine excluding packaging material.

Traditional Medicine

"Traditional medicine" means any medicinal product for human use consisting of



active ingredients derived from natural sources (plants, animals and/or minerals) used in the system of traditional practice. It shall not include any sterile preparation, vaccines, any substance derived from human parts, any isolated and characterised chemical substances.

Disclaimer: The official definition of Traditional Medicine found in The ASEAN Agreement on Traditional Medicine Products shall be referred to if there are any discrepancies.

Verification

Confirmation, through the provision of objective evidence, that the requirements for any procedure, process, equipment, material, activity or system have been fulfilled.



APPENDIX 1: LIST OF INTERNATIONALLY ACCEPTED REFERENCES FOR TEST METHODS

1. Internationally accepted Pharmacopoeia including European Pharmacopoeia, US Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia
2. American Herbal Pharmacopoeia (AHP)
3. Association of Official Analytical Chemist International: Official Methods of Analysis.
4. Microbiologicals: Food and Drug Administration Bacteriological Analytical Manual
5. WHO – Quality Control Methods for Herbal Materials, 1998 (first version) and update version
6. Standard of ASEAN Herbal Medicines (SAHM) Volume I & II
7. TLC Atlas of Chinese Crude Drugs in Pharmacopeia of The People's Republic of China Vol. 1

Note:

The use of this list is subject to the consideration, regulations and prerogative of each national regulatory authority. Other references may be considered by national regulatory authority, provided that the test methods are validated against guidelines/parameters defined by ICH / ASEAN Guidelines for Validation of Analytical Procedures.



APPENDIX 2 – VERIFICATION

PRINCIPLE

- 1.0 This Appendix describes the principles of verification which are applicable to the manufacture of traditional medicines (TM) products.

Accordingly, and in this Appendix, verification shall refer to the documented act or conduct of confirmation that the control or procedure required in a particular critical aspect of manufacturing operation has been complied with or satisfactory implemented by the manufacturer based on risk assessment and risk management.

Re-verification shall be performed if there are significant changes to the facilities, systems, processes and equipment that may have impact on the quality of the finished products, and the changes would require regulatory approval. Where there are no significant changes, periodic review shall be performed to show that the facilities, systems, processes and equipment continue to meet the prescribed requirements.

DOCUMENTATION

- 2.0 A Verification Programme which includes written procedure(s) shall be established to specify how the verification activities will be carried out. The documentation provided will demonstrate the quality assurance (QA) systems needed to produce quality traditional medicines. This includes the QA systems, which consist of elements that address matters such as roles and responsibilities, employee training, document management, equipment calibration and maintenance, manufacturing and laboratory control procedures, and product shelf life evaluation.

A report that cross-references the verification programme and procedure shall be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including the recommending changes necessary to correct the deficiencies.

VERIFICATION OF MACHINERY AND EQUIPMENT

- 3.0 Equipment and machinery shall be periodically verified to determine if they are still operating in a valid state.



During verification it is important to use calibrated reference material e.g. NIST traceable calibrated thermometer to verify the temperature of process to determine its valid state.

Machinery and equipment to be used shall have been verified prior to the verification of process and staff taking part in verification work shall have been appropriately trained.

VERIFICATION OF PROCESS

4.0 General

Verification of process contributes to assuring product quality and the basic principle of quality assurance is that a product shall be produced under such condition that is fit for its intended use.

The basic principle of quality assurance is that a product shall be consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation and product specification.

- 5.0 Verification of process may involve demonstration, testing & analysis and in-process control, or other relevant to confirm that critical processes are kept under control. A process verification report shall be prepared to provide evidence that the process has been verified.

a) Demonstration.

Demonstration is the operation of an item to provide evidence that it can meet its predetermined specifications and quality attributes.

Demonstrations can be conducted in actual or simulated environments.

b) Testing & Analysis

Test is the application of scientific principles and procedures to determine the properties or functional capabilities of items. Test is similar to demonstration, but is more exacting, generally requiring specialized test equipment, configuration, data, and procedure in order to verify that the item satisfies the requirement.



Analysis is the use of established technical or mathematical models or simulations, algorithms, or other scientific principles and procedures to provide evidence that the item meets its stated requirements.

c) In-process control

Critical parameters shall be determined and monitored, checks performed during production in order to monitor and if necessary to adjust the process to ensure that the products confirm to its specification. The control of the environment or equipment may also be regarded as a part of in-process control.

CHANGE CONTROL

- 6.0 Written procedures shall be in place to describe the actions to be taken if a change is proposed to a starting material, product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or reproducibility of the process. Change control procedures shall ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications.
- 7.0 All changes that may affect product quality or reproducibility of the process shall be formally requested, documented and approved by the relevant department. The likely impact of the change of facilities, systems and equipment on the product shall be evaluated, including risk analysis. The need for, and the extent of, re-verification of machinery and equipment and re-verification of process shall be determined.