GUIDELINES ON GOOD MANUFACTURING PRACTICE FOR TRADITIONAL MEDICINES AND HEALTH SUPPLEMENTS

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INTRODUCTION

Under the 'Control of Drugs and Cosmetics Regulations 1984' compliance with Good Manufacturing Practice (GMP) is required as one of the conditions to be considered in the evaluation of applications for a Manufacturing License.

Manufacture as defined in the Regulations includes:

a) the making or assembling of the product,

b) the enclosing or packing of the 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.

In the manufacture of traditional medicines and health supplements, overall control is essential to ensure that the consumer receives medicines of quality. Haphazard operations cannot be permitted in the manufacture of materials that may be necessary to restore or to preserve health. The good practices outlined in these guidelines should be considered as general guides; whenever necessary, they may be adapted to meet individual needs, provided the established standards of medicine quality are still achieved.

The production of traditional medicines and health supplements that utilize materials of natural origin such as plants and animals are prone to contamination, deterioration and variation in quality. Therefore, the control of the starting materials, storage and processing of traditional medicines and health supplements 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 and health supplements.

The manufacture of traditional medicines and health supplements depends on the starting materials, manufacturing processes, building, equipment and personnel involved. It is not sufficient that the finished product merely passes testing protocols but quality must also be built into the product. All traditional medicines and health supplements should be manufactured under strictly controlled and monitored conditions, and sole reliance should not be placed on any test for assurance of the quality of the end product.

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

CHAPTER 1

QUALITY MANAGEMENT

PRINCIPLE

The holder of a Manufacturing License must manufacture traditional medicines and health supplements so as to ensure that they are fit for their intended use, comply with the requirements of the Product Registration and do not place 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 must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice and thus Quality Control. It should be fully documented and its effectiveness monitored. All parts of Quality Assurance system should be adequately resourced with competent personnel, and 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 and health supplements.

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 medicinal product are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide.

The system of Quality Assurance appropriate for the manufacture of traditional medicines and health supplements should ensure that:

i. traditional medicines and health supplements are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice;

ii. production and control operations are clearly specified and Good Manufacturing Practice adopted;

iii. managerial responsibilities are clearly specified;

iv. arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;

v. all necessary controls on intermediate products, and any other in-process controls;

vi. the finished product is correctly processed and checked, according to the defined procedures;

vii. traditional medicines and health supplements are not sold or supplied before a head of Quality Control has certified that each production batch has been produced and controlled in

accordance with the requirements of the Product Registration and any other procedures relevant to the production, control and release of traditional medicines and health supplements;

viii. satisfactory arrangements exist to ensure, as far as possible, that the traditional medicines and health supplements are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;

ix. there is a procedure for Self-Inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Quality Assurance system.

GOOD MANUFACTURING PRACTICE (GMP) FOR TRADITIONAL MEDICINES AND HEALTH SUPPLEMENTS

1.3 Good Manufacturing Practice is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Product Registration or product specification.

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

i. all manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing traditional medicines and health supplements of the required quality and complying with their specifications;

ii. critical steps of manufacturing processes and significant changes to the process are verified or validated;

iii. all necessary facilities for GMP are provided including:

a. appropriate qualified and trained personnel;

b. adequate premises and space;

c. suitable equipment and services;

d. correct materials, containers and labels;

e. approved procedures and instructions;

f. suitable storage and transportation;

iv. instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;

v. operators are trained to carry out procedures correctly;

vi. 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;

vii. records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

viii. the distribution of the products minimises any risk to their quality;

ix. a system is available to recall any batch of product, from sale or supply;

x. 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 reoccurrence.

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:

i. adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing of starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental

conditions for GMP purposes;

ii. samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control;

iii. test methods are validated;

iv. 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;

v. the finished products contain active materials complying with the qualitative and quantitative composition of the Product Registration, are of the quality required, and are enclosed within their proper containers and correctly labelled;

vi. 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;

vii. no batch of product is released for sale or supply prior to certification by a head of QC that it is in accordance with the requirements of the Product Registration;

viii. 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

1.4 Regular periodic or rolling quality reviews of all registered traditional medicines and health supplements, including export only products, should 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 should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

i. A review of starting materials and packaging materials used for the product, especially those from new sources.

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ii. A review of critical in-process controls and finished product results.

iii. A review of all batches that failed to meet established specification(s) and their investigation.

iv. A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.

v. A review of all changes carried out to the processes or analytical methods.

vi. A review of product registration requirement variations

submitted/granted/refused, including those for third country (export only) dossiers.

vii. A review of the results of the stability monitoring programme and any adverse trends.

viii. A review of all quality-related returns, complaints and recalls and the investigations performed at the time.

ix. A review of adequacy of any other previous product process or equipment corrective actions.

x. The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.

xi. A review of Technical Agreements to ensure that they are up to date.

xii. For new product registrations and variations to product registrations, a review of post-marketing commitment.

CHAPTER 2

PERSONNEL

PRINCIPLE

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

ORGANISATION, QUALIFICATION AND RESPONSIBILITIES

2.1 The manufacturer must have an organisation chart. People in responsible positions should 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 should 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 are headed by different persons; neither of who shall be responsible to the other. Each should be given full authority necessary to execute his duties effectively.

2.2 The head of Production Department should be adequately trained and possess good practical experience and adequate knowledge in manufacturing traditional medicines and health supplements, which can enable him to perform his functions effectively.

The head of Production Department should 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:

i. to ensure those products are produced and stored according to the appropriate documentation in order to obtain the required quality;

ii. to approve the instructions relating to production operations, including the in-process controls and to ensure their strict implementation;

iii. to ensure that the production records are evaluated and signed by a designated person before they are made available to the Quality Control Department;

iv. to check the maintenance of the department, premises and equipment;

v. to ensure that the critical processes are appropriately verified or validated;

vi. 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 should have adequate training and practical experience, which can enable him to perform his functions effectively. He should be given full authority and responsibility in all Quality Control duties such as establishment, verification and implementation of all Quality Control procedures. He should 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 should have the following responsibilities:

i. to approve or reject starting materials, packaging materials and intermediate, bulk and finished products;

ii. to evaluate batch records;

iii. to ensure that all necessary testing is carried out;

iv. to ensure that the critical processes are appropriately verified or validated;

v. to approve sampling instructions, specification, test methods,

and other Quality Control procedures;

vi. to approve and monitor tests carried out under contract;

vii. to check the maintenance of the department, premises and equipment;

viii. to establish expiration date and shelf life specifications on the basis of stability test or available stability data related to storage conditions;

ix. to approve those suppliers of raw materials and packaging materials who are known or believed to be capable of reliably supplying products meeting the company's established quality standards;

x. to evaluate all complaints received or deficiencies noted about any batch, if necessary in conjunction with other departments, and to take appropriate action accordingly;

xi. to maintain adequate analytical records concerning the examinations of all samples taken;

xii. to recommend contract-manufacturing operations which should meet the company's specified quality standards;

xiii. 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 should share a joint responsibility :

i. to establish and to authorize written procedures;

ii. to monitor and control the manufacturing environment, sanitation and hygiene;

iii. to verify or validate critical processes;

iv. to train personnel;

v. to approve and monitor the suppliers of materials and contract manufacturers;

vi. to design and monitor the storage conditions for materials and products;

vii. to retain records;

viii. to monitor compliance with the requirements of Good Manufacturing Practice;

ix. to inspect, investigate and take samples, in order to monitor factors which may affect product quality.

2.5 An adequate number of trained personnel should be available to carry out the production and the quality control operations in accordance

with established procedures and specifications.

TRAINING

2.6 All personnel who are directly engaged in the manufacturing activities should be trained in the particular operations and in the principles of Good Manufacturing Practice.

2.7 Training in Good Manufacturing Practice should 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 should be in accordance with written programmes approved by the head of Production Department and the head of Quality Control Department.

2.8 Records of personnel training in Good Manufacturing Practice should be maintained and the effectiveness of training programs should be assessed periodically. After training, the employees' performance should be appraised to determine whether they have proper experience for the jobs assigned to them.

2.9 The concept of Quality Assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

PERSONAL

2.10 All personnel, prior to employment, should undergo health examinations. During the course of their employment they should also

routinely undergo health examinations which should include relevant examinations appropriate to the tasks that they are required to perform such as periodic eye examination.

2.11 All personnel should practice good personal hygiene. They should be trained in the practice of personal hygiene. High level of personal hygiene should be observed by all those concerned with manufacturing processes.

2.12 Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle raw materials, packaging materials, in-process materials and finished products until the condition is improved.

2.13 All personnel should be instructed and encouraged to report to their immediate supervisor any circumstances (e.g. plant, equipment or personnel) that they consider may adversely affect the products.

2.14 Direct contact should be avoided between the operator's hands and raw materials, intermediate or bulk product. Appropriate gloves should be used if contact with hands is unavoidable.

2.15 To assure protection of the product from contamination as well as the safety of the personnel, they should wear clean full garments appropriate to the duties they perform, including appropriate hair covers and shoes. Soiled uniforms should be stored in closed containers until properly laundered. Manufacturers are encouraged to have in-house laundry for cleaning garments used in production area.

2.16 Only authorized personnel should be allowed to enter production areas.

2.17 Smoking, eating, drinking and chewing or keeping of plants, food, drink, smoking materials, and personal medicines should be restricted to specific areas and not permitted in production, laboratory, storage or other areas where they might adversely influence product quality.

2.18 The wearing of make-up, wrist watches and jewellery should be prohibited in the production area.

2.19 Visitors or untrained personnel should, preferably, not be taken into the production and quality control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

CHAPTER 3

PREMISES AND EQUIPMENT

PRINCIPLE

Because of their often complex and variables nature, and the number and small quantity of defined active materials, control of starting materials, storage and processing assume particular importance in the manufacture of traditional medicines and health supplements.

PREMISES

GENERAL

3.1 The premises for manufacturing should be of suitable size, design, construction and location to facilitate proper operation, cleaning and maintenance. The individual working areas must be adequate so that any risk of confusion, cross-contamination and other mistakes that could adversely affect the quality of the products could be avoided.

3.2 Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

3.3 All premises, including production area, laboratories, stores, passage

ways and external surroundings should be maintained in a clean and tidy condition.

LOCATION AND DESIGN

3.4 Premises must be located at a suitable site approved or in accordance with the relevant authorities.

3.5 Premises should be so located as to avoid contamination from the surrounding environment such as air, earth and water pollutants as well as from other nearby activities. Should it occur that the premises are unsuitably located, effective measures should be taken to avoid such contamination.

3.6 The manufacturing of traditional medicines and health supplements should be done in separate facilities. However, if the issue of cross-contamination can be adequately addressed, sharing of manufacturing facilities may be considered.

3.7 Premises should be so constructed and maintained to protect against weather, flood, ground seepage and the access and harbouring of vermin, rodents, birds, insects or other animals.

3.8 In determining the design and layout of premises, consideration should be paid to:

i. the compatibility of other manufacturing operations that may be carried out in the same or neighbouring premises;

ii. the adequacy of the working space, which should 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;

iii. avoiding the use of production areas for general traffic of personnel or materials or for storage other than of materials in process;

3.9 The design and layout of premises should fulfil the following requirements:

i. the processing of materials or products which are not intended for human use must be separated from the production area of the traditional medicines and health supplements;

ii. the risk of mix-up between different products or their components, the possibility of cross-contamination by other substances and the risk of omission of any production step should be prevented;

Special attention must be given for processing products that generate dust such as powders. Dust must be contained within the room. Suitable dust extraction and air handling systems will help to achieve the desired differential pressure and net airflow.

iii. the separation of production operations can be achieved by provision of a separate building or by effective isolation of the

operations within a single building;

a. changing rooms should be directly connected to but separated from processing areas;

b. toilets, rest and refreshment rooms should not be in the manufacturing areas;

c. laboratories should be physically separated from the production areas. In-process quality controls (IPQC) may be carried out within the production area provided they do not carry any risk for the production;

d. maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

3.10 Defined areas for the following operations are required:

i. incoming goods and quarantine;

ii. storage of starting materials;

iii. weighing and dispensing;

iv. processing;

v. storage of bulk products;

vi. packaging;

vii. quarantine storage before final release of products;

viii. storage of finished products;

ix. laboratories;

x. equipment washing.

PRODUCTION AREAS

3.11 Interior surfaces (walls, floors and ceilings) should be

i. smooth and free from cracks and open joints;

ii. should not retain and shed particulate matter;

iii. should permit easy cleaning and if necessary disinfecting.

The floor in processing areas should be made of impervious materials, laid to an even surface and should allow prompt and efficient removal of any spillage. Walls should be of impervious and washable surface. The coving of junctions between walls and floors in the production areas is encouraged to facilitate cleaning.

3.12 Any open channels should be avoided where possible, but if required they should be shallow enough to facilitate cleaning and disinfecting.

The channel should be of suitable material. All drainage outlets should have suitable trapped gullies.

3.13 Buildings should be effectively lit and ventilated with air control facilities (including temperature, humidity and filtration), appropriate both to the operations undertaken within them and to the external environment.

3.14 Pipework, light fittings, ventilation points and other services in manufacturing areas should be installed in such a way as to avoid uncleanable recesses and preferably run outside the processing areas.

3.15 The production of external and internal products must be carried out in separate rooms.

3.16 The condition of buildings should be reviewed regularly, and repaired where necessary. Special care should be exercised to ensure that building repair or maintenance operations do not adversely affect, directly or indirectly, either the traditional medicines and health supplements during their manufacture and storage, or the accurate functioning of equipment.

3.17 Specific provisions should be taken during sampling, weighing, mixing and processing operations of crude natural materials whenever dust is generated, to facilitate cleaning and to avoid cross-contamination, as for example, dust extraction system, dedicated premises, etc.

STORAGE AREAS

3.18 Storage areas should be of adequate space, provided with suitable lighting, arranged and equipped to allow dry, clean and orderly placement of stored materials and products.

3.19 Such areas should be suitable for effective separation of quarantined, recalled/returned, rejected and approved/passed materials and finished products.

3.20 Special and segregated areas should be available for storage of flammable and explosive substances, highly toxic substances, rejected and recalled materials and products.

3.21 Crude (i.e. unprocessed) natural materials should be stored in separate areas. The store area should be well ventilated and equipped in such a way as to give protection against insects, or other animals, especially rodents. Effective measures should 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 should be located in such a way as to allow free air circulation.

3.22 Special attention should be paid to the cleanliness and good maintenance of the storage areas particularly when dust is generated.

3.23 Storage of plants, extracts, tinctures and other preparations may require special conditions of temperature, humidity or light protection; these conditions should be provided and monitored.

3.24 Storage areas should be laid-out to permit effective and orderly segregation of the various categories of materials stored, and to allow rotation of stock.

3.25 Labels and other printed materials should be stored in a proper manner to avoid mix-up.

3.26 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

3.27 All quarantined material should be stored in a restricted area accessible to authorized personnel only.

3.28 Different enclosed and well ventilated areas should be used to quarantine incoming materials of natural origin and for the approved materials of natural origin.

3.29 There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

QUALITY CONTROL AREAS

3.30 Laboratories or quality control areas should be separated from production areas. There should be adequate suitable storage space for

samples and records.

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CLEANING AND SANITISATION OF PREMISES

3.31 Premises used for the manufacturing of products should be of suitable design and construction so as to facilitate good sanitation.

3.32 Adequate employee's washing and well ventilated toilet facilities and changing rooms should be provided at suitable locations.

3.33 Changing rooms into the production areas should have adequate hand washing facilities.

3.34 Suitable locker facilities should be provided at appropriate locations for the storage of employees clothing and personal property.

3.35 The preparation, storage and consumption of food and beverages should be restricted to specific areas, such as canteen. Facilities in such rooms must meet sanitary standards.

3.36 All cleaning utensils used in the production area must not cause a potential risk of contamination.

3.37 Waste material should not be allowed to accumulate. It should 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.

3.38 Rodenticides, insecticides, fumigating agents and sanitising materials

must not be permitted to contaminate equipment, raw materials, packaging materials, in-process materials or finished products.

3.39 There should 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 should be followed.

3.40 Animals including pets are not allowed within the vicinity of the manufacturing plant.

EQUIPMENT

3.42 Manufacturing equipment should be adequate for the operations performed and should be designed, constructed, placed and maintained in such a way to:

i. be suitable for its intended use (where possible stainless steel containers, utensils and piping should be used);

ii. be easily dismantled for inspection or it should be demonstrated that routine cleaning procedures eliminate the possibility of contamination;

iii. minimise any contamination, risk of confusion or the omission of a processing step during manufacturing;

iv. be located at a distance from other equipment sufficient to avoid congestion and cross-contamination;

v. fixed pipework (and valves) should be clearly identified as to their contents.

3.41 Balances and measuring equipment of an appropriate range and precision should be available for production and control operation.

3.42 Weighing and testing equipment used in manufacture and quality control should be calibrated, checked and properly recorded at regular intervals and maintained properly to enable them to perform their proper functions.

3.43 Written procedures should be established and followed for cleaning and maintenance of equipment, including utensils used in the manufacture, processing, packing or holding of traditional medicines and health supplements. Equipment should be checked for cleanliness prior to each use.

3.44 Equipment used for the preparation of internal products should be separated from that of external products.

3.45 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

3.46 Repair and maintenance operations should not present hazard to the quality of the products.

3.47 Production equipment should 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.

3.48 The equipment, filtering materials etc. used in the manufacturing processes must be compatible with the extraction solvent, in order to prevent any release or undesirable absorption of substance that could affect the product.

3.49 Pipework and hoses for treated water and products should be cleaned and sanitised according to written procedures.

CLEANING AND SANITISATION OF EQUIPMENT

3.50 Equipments and utensils should be cleaned both inside and outside after use according to established procedures and should be kept or stored in a clean condition and be checked for cleanliness prior to each use to ensure that all products or materials from the previous batch are removed.

3.51 Any missing components such as nuts, springs, clips, etc. should be reported and investigated immediately.

3.52 Vacuum or wet cleaning methods are preferred. Compressed air, fibrous material and brushes should be used with care and avoided if possible, as they increase the risk of product contamination.

3.53 Adequate space, preferably separated from processing areas, should be provided for cleaning and storing mobile equipment and the storage of

cleaning materials.

3.54 Written procedures should be established and followed for cleaning and sanitising equipments, utensils and containers used in the manufacture of traditional medicines and health supplements.

3.55 These procedures should be designed to prevent equipment contamination by cleaning or sanitising agents and should at least include the following:

i. responsibility for cleaning,

ii. cleaning schedule,

iii. cleaning methods,

iv. equipment and materials used in cleaning operations,

v. methods of disassembling and reassembling equipment.

vi. removal of previous batch identification

vii. protection of clean equipment and utensils from contamination prior to use.

3.56 Records of cleaning, where appropriate sanitising and inspection prior to use should be maintained.

CHAPTER 4

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 traditional medicines and health supplements, from starting materials to the finished products. It should 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 which is consists of manufacturing formulae and instructions, specifications, procedures and records must be free from errors and available in writing.

GENERAL

4.1 The system of documentation should be able to record the complete history of each batch. It should be adequate to permit investigation and tracing of defective products.

4.2 Documents should contain all necessary information, but no

superfluous data, to be kept up to date and any amendment should be formally authorised. It should include provision for periodic review and revision as necessary.

4.3 The production records and the reference samples of starting materials and finished products should be retained for one year after the expiry dates.

4.4 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and Product Registration dossiers.

4.5 Documents should be approved, signed and dated by appropriate and authorised persons.

4.6 Documents should have unambiguous contents; title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and should also be easy to checked. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

4.7 Documents should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.

4.8 Documents should not be hand-written; although, where documents require the entry of data, these entries may be made in clear, legible, indelible handwriting. Sufficient space should be provided for such

entries.

4.9 Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

4.10 The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of traditional medicines and health supplements products are traceable. They should be retained for at least one year after the expiry date of the finished product.

4.11 Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedure relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data processing methods, only authorised persons should be able to enter or modify data in the computer and there should be a record of changes and deletions; access should be restricted by passwords or other means and the result of entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper or other means. It is particularly important that the data are readily available throughout the period of retention.

QUALITY CONTROL DOCUMENTS

4.12 The following details should be readily available to the Quality

Control Department:

i. specifications;

ii. sampling procedures;

iii. testing procedures and records;

iv. worksheets and/or laboratory notebooks ;

v. analytical reports and/or certificates;

vi. data from environmental monitoring, where required;

vii. procedures for and records of the calibration of instruments and maintenance of equipment.

4.13 Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch.

Specifications

4.14 The starting materials used in traditional medicines and health supplements should be manufactured in accordance with GMP and the Product Registration dossier. Comprehensive documentation on audits of the starting material suppliers carried out by, or on behalf of the manufacturer should be made available. The audit trail of the active ingredient is fundamental to the quality of starting material. The manufacturer should ensure that the suppliers of the starting materials

are in compliance with acceptable standards.

There should be appropriately authorised and dated specifications for starting materials, packaging materials and finished products and where appropriate, they should be also available for intermediate or bulk products.

Specification for Natural Materials

4.15 The specifications for materials of natural origin should as far as possible include the following:

i. scientific name or botanical name for plant; and if possible with reference to the authors;

ii. details to the source of the plant (country or region of origin, and where applicable, cultivation, time of harvesting, collection procedures, possible pesticides used, etc.);

iii. whether the whole plant/animal or only a part is used;

iv. when dried plant/animal is purchased, drying system should be specified;

v. description of plant material, macroscopical and/or microscopical visual inspection.

4.16 Testing procedures should be available if the following tests are conducted:

i. identification tests including, where possible, identification tests for known active constituents, or markers;

ii. assay, where possible, of constituents of known and unknown therapeutic activity or markers;

iii. limit tests such as extractive value, ash value, and presence of essential oils and loss on drying;

iv. determination of pesticide contamination and limits accepted;

v. tests for toxic metals and for likely contaminants, foreign materials and adulterants;

vi. tests for radioactivity, aflatoxin, and microbial contamination;

vii. any treatment used to reduce fungal/microbial contamination or other infestation should be documented.

Specifications for Starting and Packaging Materials

4.17 Specifications for starting and primary or printed packaging materials should include, if applicable:

i. a description of the materials, including:

a. the designated name and the internal code reference;

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

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

d. a specimen of printed materials;

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

iii. qualitative and quantitative requirements with acceptance limits;

iv. storage conditions and precautions;

v. the maximum period of storage before re-examination.

Specifications for Intermediate and Bulk Products

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

Specification for Finished Products

4.19 The specifications for finished product may include the following tests:

i. microbial and toxic metals contamination;

ii. uniformity of weight (for tablets and capsules), disintegration (for tablets, capsules and pills), hardness and friability (for tablets), and viscosity (for internal and external fluids);

iii. physical appearance such as colour taste and size.

4.20 The specifications should also include:

i. the designated name of the product and the code reference where applicable;

ii. the formula or a reference to;

iii. a description of the dosage form and package details;

iv. directions for sampling and testing or a reference to procedures;

v. the qualitative and quantitative requirements, with the acceptance limits;

vi. the storage condition and any special handling precautions, where applicable;

vii. the shelf-life.

PRODUCTION DOCUMENTS

Manufacturing Formula and Processing Instructions

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

4.21 The Manufacturing Formula should include:

i. the name of the product, with a product reference code relating to its specification;

ii. a description of the dosage form, strength of the product and batch size;

iii. 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 should be made of any substance that may disappear in the course of processing;

iv. a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

4.22 The Processing Instructions should include:

i. a statement of the processing location and the principal equipment to be used;

ii. the methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating);

iii. detailed stepwise processing instruction (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures);

iv. the instructions for any in-process controls with their limits;

v. where necessary, the requirements for bulk storage of the products; including the container, labelling and special storage conditions where applicable;

vi. any special precautions to be observed.

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

In particular, there should be written instructions and records, which ensure that each container of herbal substance 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.

For the production of a vegetable drug preparation, instructions should include details of base or solvent, time and temperatures of extraction,

details of any concentration stages and methods used.

PACKAGING INSTRUCTIONS

4.23 There should be formally authorised Packaging Instructions for each product, pack size and type. These should normally include, or have a reference to the following:

i. name of the product;

ii. description of its dosage form, and strength where applicable;

iii. the pack size expressed in terms of the number, weight or volume of the product in the final container;

iv. 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;

v. 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;

vi. special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;

vii. a description of the packaging operation, including any

significant subsidiary operations, and equipment to be used;

viii. details of in-process controls with instructions for sampling and acceptance limits.

BATCH PROCESSING RECORDS

4.24 Batch Processing Record is that part of Batch Manufacturing Record and should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions. The method of preparation of such records should be designed to avoid transcription errors. The record should carry the number of the batch being manufactured.

4.25 Before any processing begins, there should be recorded checks 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.

4.26 During processing, the following information should be recorded at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person responsible for the processing operations :

i. the name of the product;

ii. dates and times of commencement, of significant intermediate stages and of completion of production;

iii. name of the person responsible for each stage of production;

iv. initials of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing);

v. 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);

vi. any relevant processing operation or event and major equipment used;

vii. a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;

viii. the product yield obtained at different and pertinent stages of manufacture;

ix. notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions.

BATCH PACKAGING RECORDS

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

4.28 Before any packaging operation begins, there should 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.

4.29 The following information should be entered at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:

i. the name of the product;

ii. the date(s) and times of the packaging operations;

iii. the name of the responsible persons carrying out the packaging operation;

iv. the initials of the operators of the different significant steps;

v. records of checks for identity and conformity with the

packaging instructions including the results of in-process controls;

vi. details of the packaging operations carried out, including references to equipment and the packaging lines used;

vii. whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;

viii. notes on any special problems or unusual events including details, with signed authorisation from the Manufacturing Formula and Processing Instructions;

ix. 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

4.30 There should be written procedures and records for the receipt of each delivery of each starting and primary printed packaging material.

The records of the receipts should include:

i. name of the material on the delivery note and the containers;

ii. the " in-house" name and/or code of material (if different from

a);

iii. date of receipt;

iv. supplier's name and, if possible manufacturer's name;

v. manufacturer's batch or reference number;

vi. total quantity, and number of containers received;

vii. the batch number assigned after receipt;

viii. any relevant comment (e.g. state of the containers).

4.31 There should be written procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

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

4.33 There should be standard operating procedures for sampling, which specify the person(s) authorised to take samples, and the sampling instructions.

4.34 There should 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.

4.35 The standard operating procedures for batch numbering should assure that the same batch numbers will not be repeatedly used; this applies also to reprocessing.

4.36 Batch-number allocation should be immediately recorded, e.g. in a logbook. The record should include date of allocation, product identity, and size of batch.

4.37 The standard operating procedures for batches numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

4.38 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorised person.

4.39 Distribution records of each batch of a product should be maintained in order to facilitate the recall of the batch if necessary.

4.40 Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for:

i. equipment assembly;

ii. analytical apparatus and calibration;

iii. maintenance, cleaning, and sanitisation of equipment and

premises;

iv. personnel matters including qualification, GMP training, clothing, and hygiene;

v. environmental monitoring;

vi. pest control;

vii. adverse drug reactions, complaints and product recalls;

viii. returns and salvaged products, rejected products/materials.

4.41 Logbooks should be kept with major and critical equipment and should record, as appropriate, any calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.

4.42 There should be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used and facilities to be cleaned. Such written procedures should be followed.

4.43 Records of receipt, issue and balance of each starting material, intermediate, bulk and finished traditional medicines and health supplements should be available.

4.44 There should be written procedures for self-inspection.

4.45 Records of disposal or destruction of rejected materials should be available.

4.46 There should be written procedures for handling of returned goods.

4.47 Distribution records should be available and maintained .

4.48 Logbooks should also record in chronological order the use of major or critical equipment and the areas where the products have been processed.

4.49 Several of the above-mentioned procedures, specifications and/or records may be combined together in one specific document.

CHAPTER 5

PRODUCTION

PRINCIPLE

With the premises and equipment provided, the processes used in production should 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

5.1 Production should be performed and supervised by competent people.

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

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

5.4 Damage to containers and any other problem, which might adversely

affect the quality of a material, should be investigated, recorded and reported to the Quality Control Department.

5.5 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

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

5.7 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.

5.8 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

5.9 Operations on different products should not be carried our simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

5.10 At every stage of processing, products and materials should be protected from microbial and other contamination.

5.11 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust.

5.12 At all time during processing, all materials, bulk containers, major

items of equipment and where appropriate rooms used should 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 should also mention the stage of production.

5.13 Labels applied to containers, equipment or premises should 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.).

5.14 Checks should 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.

5.15 Access to production premises should be restricted to authorised personnel.

5.16 Production of products other than traditional medicines and health supplements should be avoided in the same production areas.

5.17 Water used as ingredients or for final rinsing of production equipment should be treated to minimise microbial contamination.

VERIFICATION OR VALIDATION

5.18 Verification or validation work, that is needed to prove control of critical aspects of particular operations should be identified. Significant changes to the facilities, equipments and the processes which may

affect the quality of the product should be verified or validated. A risk assessment approach should be used to determine the scope and extent of verification or validation.

PREVENTION OF CROSS-CONTAMINATION IN PRODUCTION

5.19 Contamination of a starting material or of a product by another material or product must 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. Cross-contamination should be avoided by appropriate technical or organisational measures, for example:

i. production in segregated area, or by campaign (separation in time) followed by appropriate cleaning;

ii. providing appropriate air-locks and air extraction;

iii. minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

iv. keeping protective clothing inside areas where products with special risk of cross-contamination are processed;

v. using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;

vi. using " closed systems" of production;

vii. testing for residues and use of cleaning status labels on equipment;

viii. specific provisions for sampling, weighing, mixing and processing operations of crude plants whenever dust is generated.

5.20 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.

STARTING MATERIALS

5.21 The purchase of starting materials is an important operation which should involve personnel who have a particular and thorough knowledge of the suppliers.

5.22 Starting materials should 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.

5.23 For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note

and the supplier's labels.

5.24 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

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

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

ii. a batch number given at receipt;

iii. where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected).

5.26 There should 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 should be identified.

5.27 Only starting materials which have been released by the Quality Control Department and which are within their shelf life should be used.

5.28 Starting materials should 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.

5.29 Each dispensed material and its weight or volume should be independently checked and recorded.

5.30 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

PROCESSING OPERATIONS: INTERMEDIATE AND BULK PRODUCTS

5.31 The processing instructions should describe the different operations carried out upon the crude natural materials such as drying, crushing and sifting, and include drying time and temperatures, and methods used to control fragment or particle size. It should also describe security sieving or other methods of removing foreign materials.

5.32 Before the introduction of a Master Formula it should be evaluated sufficiently to determine that it is suitable for routine processing operations, and the ability of the process to be reproducible.

5.33 Production personnel should follow defined and authorised procedures for every stage of each manufacturing process.

5.34 Any deviation from defined procedures must be recorded and agreed upon between the head of Production Department and the head of Quality Control Department.

5.35 Before any manufacturing begins, steps should be taken to ensure that the work area and equipment are free from any materials, products, or documents, not required for the current operation.

5.36 At all times during processing, all materials, bulk containers and major equipment used should be labeled or otherwise identified with the name of the product or material being processed, its strength [where applicable], quantity and batch number.

5.37 Before applying labels or marks to materials and equipment, all irrelevant labels or marks previously used should be removed.

5.38 The final yield of each production batch should be recorded and checked against the theoretical yield. In the event of a significant variation, steps should be taken to prevent release or further processing of the batch, until an appropriate investigation is made.

PACKAGING MATERIALS

5.39 The purchase, handling and control of primary and printed packaging material shall be accorded attention similar to that given to starting materials.

5.40 Particular attention should be paid to printed materials. They should be stored in adequately secure condition such as to exclude unauthorised access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorised personnel following an approved and documented procedure.

5.41 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

5.42 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

PACKAGING OPERATIONS

5.43 When setting up a programme for the packaging operations, particular attention should be given to minimising the risk of the cross-contamination, mix-ups or substitutions. Different products should not be packaged in closed proximity unless there is physical segregation.

5.44 Before packaging operations are begun, steps should 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 should be performed according to an appropriate checklist.

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

5.46 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

5.47 Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass

fragments and metal particles.

5.48 Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate procedure should be applied to ensure that no mix-ups or mislabelling could occur.

5.49 The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

5.50 Special care should 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.

5.51 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

5.52 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

5.53 On-line control of the product during packaging should include at least checking the following:

i. general appearance of the packages;

ii. whether the packages are complete;

iii. whether the correct products and packaging materials are used;

iv. whether any over-printing is correct;

v. correct functioning of line monitors.

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

5.54 Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed record should be kept of this operation.

5.55 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

5.56 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

FINISHED PRODUCTS

5.57 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

5.58 The evaluation of finished products and documentation which is necessary before release of product for sale are described in Chapter 6

(Quality Control).

5.59 After release, finished products should be stored as usable stock under conditions established by the manufacturer.

REJECTED, RECOVERED AND RETURNED MATERIALS

5.60 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorised personnel.

5.61 The reprocessing of rejected products should 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 should be kept of the reprocessing.

5.62 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 should be authorised beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.

5.63 The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.

5.64 Products returned from the market and which have left the control of the manufacturer should 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 should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical reprocessing to recover active ingredient may be possible. Any action taken should be appropriately recorded.

CHAPTER 6

QUALITY CONTROL

PRINCIPLE

Every manufacturing establishment should have a quality control system so designed as to ensure that traditional medicines and health supplements are manufactured in accordance with adequate conditions and procedures and will continue to meet the established specifications.

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

GENERAL

6.1 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.

6.2 The Quality Control Department should have a laboratory adequately staffed and fully equipped for performing quality control tests, required before, during and after manufacture.

6.3 In the absence of in-house laboratory, the services of external laboratory can be used to conduct quality control tests of traditional medicines and health supplements.

6.4 The quality of the final product remains the responsibility/liability of the manufacturer.

6.5 Finished products assessment should 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.

6.6 Quality Control personnel should have access to production areas for sampling and investigation as appropriate.

6.7 Quality Control personnel should have particular expertise in herbal medicinal products in order to be able to carry out identification tests and recognise adulteration, the presence of fungal growth, infestations, and non-uniformity within a delivery of crude plants, etc.

6.8 The identity and quality of starting materials and finished products should be tested.

6.9 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 should be carried out in accordance with written procedures and, where necessary, recorded.

6.10 The stability of the bulk, intermediate and finished product should 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

6.11 Due to the fact that crude drugs are an aggregate of individual natural materials and contain an element of heterogenecity, their sampling has to be carried out with special care by personnel with particular expertise. Each batch should be identified by its own documentation.

6.12 The sample taking should be done in accordance with approved written procedures that describe:

i. the method of sampling;

ii. the equipment to be used;

iii. the amount of the sample to be taken;

iv. instructions for any required subdivision of the sample;

v. the type and condition of the sample container to be used;

vi. the identification of containers sampled;

vii. the storage conditions;

viii. instructions for the cleaning and the storage of sampling equipment.

6.13 Reference samples should 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)

6.14 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn.

6.15 Reference samples from each batch of finished products should be retained till one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions.

TESTING

6.16 All testing operations described in the Product Registration dossier should be carried out according to the approved methods.

6.17 The results obtained should be recorded and checked to make sure that they are consistent with each other. Any calculations should be critically examined.

6.18 The test performed should be recorded and the records should include at least the following data:

a. name of the material or product and, where applicable, dosage form

b. batch number and, where appropriate, the manufacturers and/or supplier

c. references to the relevant specifications and testing procedures

d. test results, including observations and calculations, and reference to any certificates of analysis

e. dates of testing

f. initials of the persons who performed the testing

g. initials of the persons who verified the testing and the calculations, where appropriate

h. a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person

6.19 All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.

CHAPTER 7

CONTRACT PRODUCTION AND TESTING

PRINCIPLE

In the case of lack of production and testing facilities, Product Registration holders can have their products manufactured or tested by contract manufacturers or external laboratories.

CONTRACT PRODUCTION

7.1 Contract production must be correctly defined, agreed, and controlled in order to avoid misunderstandings that could result in a product or work of unsatisfactory quality. There must be a written contract agreement between the Contract Giver and the Contract Acceptor, which clearly establishes the duties of each party.

All arrangements for contract manufacture, including any proposed changes in technical or other arrangements, should be in accordance with registration requirements for the product concerned.

Manufacturing and distribution records and reference samples should be made available to the Contract Giver.

CONTRACT TESTING

7.2 Contract testing must be correctly defined, agreed, and controlled in order to avoid misunderstandings that could result in a test of unsatisfactory quality. There must be a written contract agreement between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The contract must clearly state the way in which the authorised person, i.e. the chemist of the Contract Acceptor, exercises his/her full responsibilities.

THE CONTRACT GIVER

7.3 The Contract Giver should 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 this guide are followed.

7.4 The Contract Giver should provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the Product Registration documents. The Contract Giver should 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.

7.5 The Contract Giver should ensure that all traditional medicines and health supplements and materials delivered by the Contract Acceptor comply with their specifications.

THE CONTRACT ACCEPTOR

7.6 The Contract Acceptor has adequate premises, equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the Contract Giver.

7.7 The Contract Acceptor should ensure that all products or materials delivered to him are suitable for their intended purpose.

7.8 The Contract Acceptor should 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 should ensure that the manufacturing and the analytical information is made available in the same way as between the original Contract Giver and Contract Acceptor.

7.9 The Contract Acceptor should refrain from any activity that may adversely affect the quality of the product manufactured/tested for the contract giver.

7.10 The Contract Acceptor should ensure that no batch of products is released for sale or supply prior to certification by an authorized person that it is in accordance with the requirements of the Product Registration.

THE CONTRACT

7.11 A contract should 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 should be drawn up by competent persons suitably knowledgeable in traditional medicines and health supplements manufacturing, analysis and Good Manufacturing Practice. All arrangement for manufacturer and analysis must be in accordance with the marketing authorization and agreed by both parties.

7.12 The contract should 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 Product Registration.

7.13 The contract should 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 should state whether or not the Contract Acceptor should take samples at the premises of the manufacturer.

7.14 Manufacturing, analytical and distribution records, and reference samples should 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.

7.15 The contract should permit the Contract Giver to visit the facilities of the Contract Acceptor.

7.16 In the case of contract analysis, the Contract Acceptor should understand that he is subject to inspection by the competent Authorities.

CHAPTER 8

DISTRIBUTION, COMPLAINTS AND PRODUCT RECALLS

PRINCIPLE

A complete and progressive recording system for the distribution of traditional medicines and health supplements should be readily available and easily followed. All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures. In order to provide for all contingencies, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

8.1. **Distribution* Records Should Contain :**

i. the name and address of the distributor

ii. number and date of delivery order

iii. the date of delivery

iv. the name of the product and its dosage form

v. the quantity of each item

vi. the batch number

Information should be readily available to conduct a prompt, accurate and efficient product recall, whenever necessary.

PRODUCT COMPLAINTS

8.2 Product complaints are usually concerned with the quality of the product such as its physical properties, or condition of its packaging. Complaints could be made to the manufacturer, verbally or in writing by consumers, distributors or the Drug Control Authority.

8.3 All complaints should be investigated and evaluated. Written procedures describing the handling of all written and verbal complaints regarding a traditional medicines or health supplements product should be established and followed. Such procedures shall include provisions for review by the Quality Control Department. A written record of each complaint should be maintained in a file designated for traditional medicine and health supplement product complaints.

8.4 A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient staff to assist him.

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

8.6 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person

responsible for Quality Control should normally be involved in the study of such problems.

8.7 Special attention should be given to establishing whether a complaint was caused because of counterfeiting.

8.8 If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch should be investigated.

8.9 All decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

8.10 Complaint records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.

8.11 The Competent Authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, or any other serious quality problems with a product.

PRODUCT RECALLS

8.12 Responsibility and procedures for recall of traditional medicines and health supplements should be established by the manufacturer to facilitate the recall of a batch from any link of the distribution chain when this becomes necessary.

8.13 Any action taken to recall a product suspected or known to be defective or hazardous, should be prompt and in accordance with a pre-determined plan. The procedures to be followed should be specified in writing and made known to all that may be concerned.

8.14 A person should be designated as responsible for execution and co-ordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organisation.

8.15 There should be established written procedures, regularly checked and updated when necessary, in order to organise any recall activity.

8.16 Recall operation should be capable of being initiated promptly and at any time.

8.17 All Competent Authorities of all countries to which products may have been distributed should be informed promptly if products are intended to be recalled because they are, or are suspected of being defective.

8.18 The distribution records should be readily available to the person (s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.

8.19 Recalled products should be identified and stored separately in a secure

area while awaiting a decision on their fate.

8.20 The progress of the recall process should be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of the products.

8.21 The effectiveness of the arrangements for recalls should be evaluated regularly.

COMPLAINTS ON ADVERSE DRUG REACTIONS

8.22 Unexpected adverse drug reactions resulting from the use of a traditional medicines and/or health supplements must be thoroughly investigated and documented. Reports of serious unexpected adverse reactions should be immediately forwarded to the Secretary, Drug Control Authority.

CHAPTER 9

SELF-INSPECTION

PRINCIPLE

9.1 The purpose of self-inspection is to review regularly the status and adequacy of the manufacturer's compliance to GMP. Self-inspection programmes are designed to seek any defects in the quality assurance system and to establish corrective actions.

9.2 To maintain strict adherence to all manufacturing procedures and prescribed controls, it is advisable for a manufacturer to appoint a properly qualified team to conduct inspections of its overall production and control procedures.

9.3 Written procedures describing the functions of the self-inspection programme should be available and followed.

9.4 Self inspection should be conducted in an independent and detailed way by designated competent person(s) from the company. Independent audits by external experts may also be useful.

9.5 All self inspection should be recorded. Reports should contain all the observation made during the inspection and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken

should 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:

Adverse Drug Reaction

Adverse drug 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 prophylactic, diagnosis or therapy of a disease.

Batch (or Lot)

A quantity of any traditional medicine or health supplement 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.

Bulk Product

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

Date of Manufacture

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

Distribution

The division and movement of products (traditional medicines and health supplements) from the premises of the manufacturer of such products, or another central point, to the end user thereof, or to an intermediate point by means of various transport methods, via various storage and/or health establishments.

Documentation

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

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 or health supplement 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.

Manufacture

The complete cycle of production and quality control of a traditional medicine or health supplement from the acquisition of all materials through all processing and subsequent packaging to the distribution or release of the finished product.

Markers

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

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.

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 or health supplement, such as containers, closures, bags, packing, label materials [labels, inserts, etc.], seals, binding materials, adhesives and tapes.

Quality Control

All measures undertaken during manufacturing designed to ensure the uniform output of traditional medicines and health supplements that conform to established specifications of identity, purity, strength and other characteristics.

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 and health supplements.

Rejected

The status of starting materials, intermediate, bulk or finished products which are not permitted to be used for processing, packaging or distribution and should 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.

Sanitation

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

Specification

A document giving the description of a starting material, intermediate, bulk or finished product in terms of its chemical, physical and [if any] biological characteristics. A specification describes in detail the requirements with which the products or materials used or obtained during manufacture have to conform that normally includes descriptive clauses and numerical clauses, stating standards and permitted tolerances. It serves as a basis for quality evaluation.

Starting Materials

Any substance or mixture of substances used in the production of a traditional medicine or health supplement excluding packaging material.

Traditional Medicine

Any product employed in the practice of indigenous medicine to treat, mitigate, cure and prevent disease in human and to maintain human health, whereby the drug used only consists of one or more naturally occurring substances of plant, animal and mineral or part thereof, or in extracted form or non-extracted form, and any homeopathic medicine.

REFERENCES

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2. Good Manufacturing Practice for Traditional Medicines; 2nd Edition; 2003

3. Volume 4; EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use; Draft Annex 7; Manufacture of Herbal Medicinal Products

4. Council for Responsible Nutrition; Guidelines for Good Manufacturing Practice for Manufacturers of Food Supplements