Draft Code of Manufacturing Practice

Natural Health Products

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# Introduction

## The Natural Health Products Regulatory Regime

* + 1. The Natural Health Products (NHP) regulatory regime is designed to address three main risks associated with natural health products:
* the ingredients in the product could be unsafe
* consumers could be diverted from appropriate health treatment
* products could be manufactured in an unsafe way.
  + 1. These risks are addressed by:
* ingredients having to be selected from a large permitted ingredients list
* controls on health claims, and labelling
* setting robust manufacturing standards.

## Why a Code of Practice for Manufacture is needed

* + 1. The requirement for the Authority to establish a code of practice for the manufacture of NHPs (the Code) is set out in the Natural Health Products Bill (the Bill).
    2. The Bill provides that the NHP Authority must issue a Code to come into force no later than one year after commencement of the legislation.
    3. The full regulatory scheme will be phased in over three years after the legislation comes into force.
    4. All product notifiers and manufacturers have a responsibility to ensure that their NHPs are manufactured in a way that ensures consumers are not put at undue risk due to a lack of quality control during manufacture, and that they meet the minimum standards of safety, as defined by the Bill.
    5. To achieve this, the manufacturing facility must have a well-defined quality assurance system that incorporates the principles of good manufacturing practice (GMP), and the interrelated concepts of quality control and quality risk management. It should be fully documented and be monitored for effectiveness.
    6. A quality assurance system incorporates wide-ranging concepts covering all matters that individually or collectively influence the quality of a NHP. The term quality control refers to all the procedures undertaken to ensure the quality and uniformity of manufacture of a particular NHP. In regard to manufacture, quality risk management can be described as the systematic process for the assessment, control, communication and review of risks to the quality of NHPs.

Figure 1: Natural Health Product Regulatory Scheme

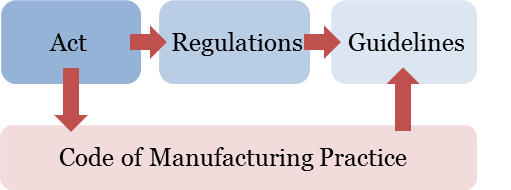


Figure 1 demonstrates how the Code forms an integral part of the regulatory scheme, and together with the regulations and guidelines, will help to ensure the safety of natural health products for consumers.

## Good manufacturing practice principles

* + 1. GMP is the part of quality assurance that ensures products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the product notification or product specification. GMP is concerned with both production and quality control. Following are the basic requirements of GMP.
* All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing products of the required quality and complying with their specifications.
* Critical steps of manufacturing processes and significant changes to the process are validated.
* All necessary facilities for GMP are provided, including:
* appropriately qualified and trained personnel
* adequate premises and space
* suitable equipment and services
* correct materials, containers and labels
* approved procedures and instructions
* suitable storage and transport
* recording and investigation of any significant deviations
* comprehensible and accessible records of manufacture, including distribution, which enable the complete history of a batch to be traced
* distribution (wholesaling) methods that minimise any risk to product quality
* a system for the recall any batch of product, from sale or supply
* a system for investigating and resolving complaints about marketed products
* investigation of the causes of quality defects, appropriate measures taken in respect of the defective products and to prevent recurrence.
  + 1. As further background to quality risk management and quality assurance, manufacturers may find the ISO 9001 series on quality management informative and useful.

## Basing the Code of Manufacturing Practice on GMP principles

* + 1. The Code includes provisions related to developing systems and procedures that fulfil the principles and that cover all the following areas:
* personnel
* premises and equipment
* production
* quality management and quality control
* complaints and recalls.

Figure 2: Components of requirements for an NHP quality assurance system

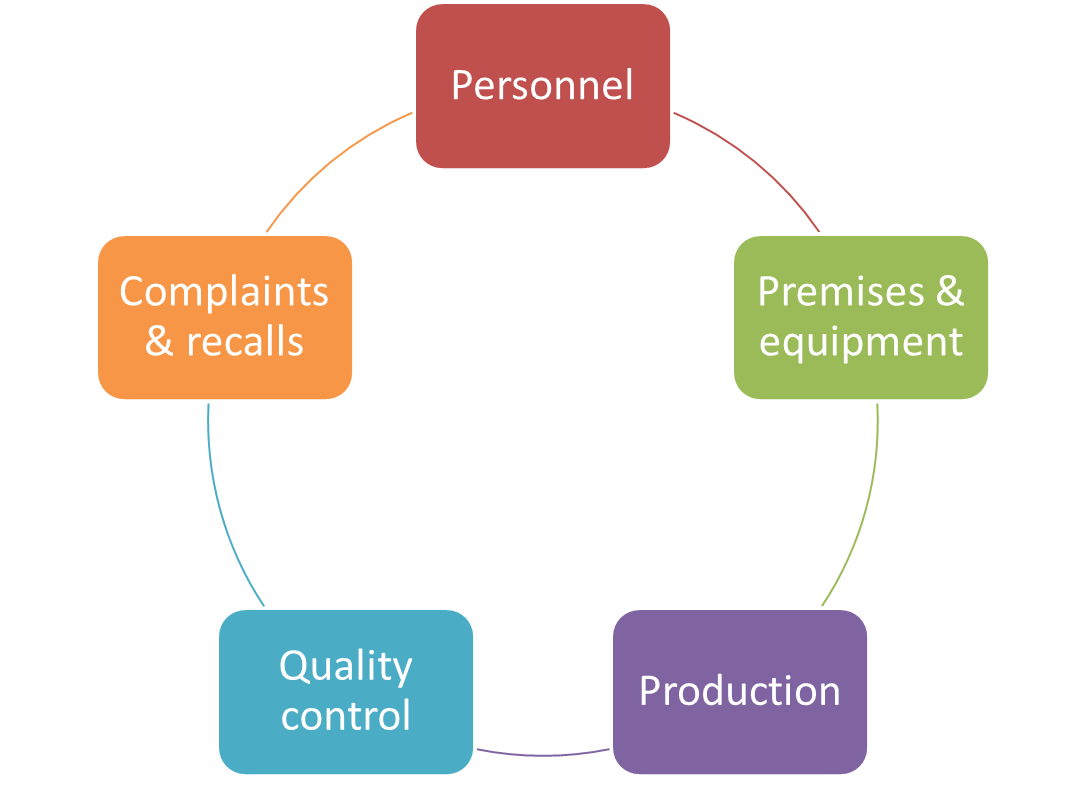


Figure 2 shows the interconnecting relationship between the components of a quality assurance system for NHPs that covers all areas relevant to an effective GMP principle-based Code. All manufacturing facilities will be required to develop, maintain and hold documentation to demonstrate that they have an appropriate quality risk management system in place covering all areas as indicated.

## Sections of the Code

* + 1. The Code is split into the following sections.
* Section 2 describes the detail of the manufacturing practice relevant to personnel, premises and equipment used, quality control measures in place, production and supporting documentation.
* Section 3 describes the detail for the management of complaints and recalls.
* Section 4 describes the detail for contract manufacture and analysis.
* Section 5 describes the detail for the collection and identification of starting materials of herbal and animal origin.
* Section 6 describes the detail for testing requirements to be included on specifications for particular dose forms.
* Section 7 provides a list of the standards and guidelines from which this Code is drawn.
  + 1. The Code should be read in conjunction with the Natural Health Products Code of Manufacturing Practice Guidelines (the Guidelines). The Guidelines will assist with interpretation and application of the Code. The Guidelines include:
* a risk assessment matrix, which allows users to broadly assess the risks arising from the product and its manufacture; it is not designed to be a prescriptive tool providing a definitive ‘risk classification’
* case studies, which describe a scenario and its key product and manufacturing attributes and a summary of some of the key considerations of application of the Code
* information about audits
* question and answer guidance.

## Other legislation to read in conjunction with this Code

* + 1. Other legislation that your products must comply with include, but are not limited to the:
* Animal Products Act 1999
* Food Act 2014 and its associated Standards
* Fair Trading Act 1986
* Hazardous Substances and New Organisms Act 1996
* Medicines Act 1981 and the Medicines Regulation 1984
* Misuse of Drugs Act 1975
* Psychoactive Substances Act 2013 and the Psychoactive Substances Regulations 2014.

# Manufacturing practice requirements

## Introduction

* + 1. This section outlines the outcomes to be achieved under the Code. It is the responsibility of the manufacturer to understand the requirements within the context of their manufacturing circumstances.

The requirements that all manufacturers must achieve are stipulated as outcomes and are highlighted in text boxes.

Each section has guidance which describes best practice for how the outcome can be achieved. Whether the best practice applies is dependent on the individual manufacturing circumstances.

## Personnel

The manufacturer has an adequate number of personnel with the necessary qualifications and practical experience to ensure the quality of a product.

### General

* + 1. A good quality assurance system that ensures the consistent quality of manufacture of NHPs relies upon people.
    2. There are sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer.
    3. Individual responsibilities are clearly understood by the individuals and are written into the supporting documentation.
    4. The manufacturer has an organisation chart.
    5. The responsibilities placed on any one individual do not present any risk to quality.
    6. People in responsible positions 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 are no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of the principles of GMP.

### Key personnel

There is a clear separation between the quality and production responsibilities. Documentation defines the key production and quality responsibilities.

* + 1. Key personnel and their responsibilities are documented. Documentation includes the person in charge of production, the person in charge of quality control, and the person in charge of releasing products for supply. Where practicable, these are different people, and key posts are occupied by full-time personnel.
    2. In large organisations it may be necessary to delegate some of these functions. In small organisations it may be difficult to have separate personnel for these key roles, depending on the number of employees.

### Production personnel

* + 1. The person in charge of production generally has responsibility to:
* ensure that products are manufactured and stored according to approved instructions
* ensure production records are correct before they are sent to the quality control person
* check that the appropriate validations (where required) are done
* ensure that the required initial and ongoing training of the production department personnel is carried out and adapted according to need
* check the maintenance of the department, premises and equipment.

### Quality control personnel

* + 1. The person in charge of the quality control aspect generally has responsibility to:
* approve or reject starting materials, packaging materials, and intermediate, bulk and finished products
* evaluate batch records
* ensure that all necessary testing is carried out
* approve specifications, sampling instructions, test methods and other quality control procedures
* approve and monitor any contract analysts
* check the maintenance of the department, premises and equipment
* ensure that the appropriate validations (if necessary) are done
* ensure that the required initial and ongoing training of the quality control department personnel is carried out and adapted according to need.
  + 1. Other duties of the quality control function are summarised in section 2.7.

### Additional responsibilities

* + 1. The people in charge of production and quality control generally have some shared responsibilities relating to quality. These may include:
* authorisation of written procedures and other documents, including amendments
* monitoring and control of the manufacturing environment
* hygiene of personnel, premises and equipment
* process validation
* training
* approval and monitoring of suppliers of materials
* approval and monitoring of contract manufacturers
* designation and monitoring of storage conditions for materials and products
* retention of records
* monitoring of compliance with the principles of GMP
* inspection, investigation and taking of samples, in order to monitor factors which may affect product quality.

### Training

Training programmes are in place to ensure that staff activities and visitors or untrained personnel do not present a risk to the quality of a product.

* + 1. Besides basic training on the theory and practice of GMP, newly recruited personnel receive training appropriate to their duties.
    2. The manufacturer provides training for all the personnel whose duties take them into production areas or into control areas (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.
    3. Ongoing training is given, and its practical effectiveness is periodically assessed. Training programmes are available, approved by either the person in charge of production or the person in charge of quality control, as appropriate.
    4. Personnel working in areas where contamination is a hazard, such as clean areas or areas where highly active, toxic, infectious or sensitising materials are handled, are given specific training.
    5. The concept of quality assurance and all the measures capable of improving understanding and implementation is fully discussed during the training.
    6. Training records are kept.
    7. It is preferable that visitors or untrained personnel are not taken into the production and quality control areas. If this is unavoidable, they are given information in advance, particularly about personal hygiene and appropriate protective clothing. They are closely supervised.

### Personal hygiene

Hygiene programmes are in place. They include procedures relating to the health, hygiene practices and clothing of personnel.

* + 1. These procedures are understood and followed by everyone with responsibilities in production and control areas.
    2. Hygiene programmes are promoted by management and widely discussed during training sessions.
    3. All personnel receive a medical examination upon recruitment, if appropriate. After this, medical examinations are be carried out when necessary for the work and personal health. Steps are taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of their body is engaged in the manufacture of NHPs. Staff and management are all responsible for ensuring that management is made aware when a staff member has a health condition that could affect the quality of products.
    4. Every person entering the manufacturing area wears protective garments appropriate to the operations to be carried out.
    5. Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication, in the production and storage areas is not permitted.
    6. Any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected is not permitted.
    7. Direct contact is avoided between the operator’s hands and the exposed product as well as with any part of the equipment that comes into contact with the products.
    8. Personnel are instructed to use the hand-washing facilities.

## Premises

Premises are located, designed, constructed, adapted and maintained to suit the operations to be carried out.

The layout and design of premises minimises the risk of errors, and permits effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of a product.

### General

* + 1. Premises are situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products. Premises are carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They are cleaned and, if applicable, disinfected according to detailed written procedures.
    2. Lighting, temperature, humidity and ventilation are appropriate and such that they do not adversely affect, directly or indirectly, the NHPs during their manufacture and storage, or the accurate functioning of equipment. Premises are designed and equipped so as to offer maximum protection against the entry of insects or other animals.
    3. Steps are taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas are not used as a right of way by personnel who do not work in them.

### Manufacture of a range of products

* + 1. If a facility manufactures a wide range of products (for example, both medicines and NHPs), certain additional products (such as certain hormones, cytotoxics, highly active substances and drugs) and health products that do not meet the definition of a NHP should not be produced in the NHP manufacturing facility.
    2. The manufacture of technical poisons, such as pesticides and herbicides, should not be produced in the NHP manufacturing facility.
    3. Different batches of the same product can be made in sequence (the principle of campaign working) in the same facilities provided that specific precautions are taken and the necessary validations are made between batches.

### Production area

* + 1. Premises are laid out to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
    2. The adequacy of the working and in-process storage space permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different NHPs or their components, to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.
    3. Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) are smooth, free from cracks and open joints, and do not shed particulate matter and permit easy and effective cleaning and, if necessary, disinfection.
    4. Pipe work, light fittings, ventilation points and other services are designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they are accessible from outside the manufacturing areas.
    5. Drains are of adequate size, and have trapped gullies. Open channels are avoided where possible, but if necessary, they are shallow to facilitate cleaning.
    6. Production areas are effectively ventilated, with air control facilities (including where necessary, temperature, humidity and filtration) appropriate to the products handled, to the operations undertaken within them and to the external environment.
    7. Weighing of starting materials are carried out in a separate weighing room designed for that use.
    8. If dust is generated (such as during sampling, weighing, mixing and processing operations, and packaging of dry products), specific measures are taken to avoid cross-contamination and facilitate cleaning.
    9. Premises for the packaging of NHPs are designed and laid out so as to avoid mix-ups or cross-contamination.
    10. Production areas are well lit, particularly where visual production line controls are carried out.
    11. In-process controls are carried out within the production area provided they do not carry any risk for the production.

### Storage areas

* + 1. Storage areas are of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.
    2. Storage areas are designed or adapted to ensure good storage conditions. In particular, they are clean and dry, and maintained within acceptable temperature limits. If special storage conditions are required (such as temperature or humidity) these are provided, checked and monitored.
    3. Receiving and dispatch bays protect materials and products from the weather. Reception areas are designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.
    4. If quarantined products are stored in separate areas, these areas are clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine is given equivalent security.
    5. If sampling is performed in the storage area, it is conducted in such a way as to prevent contamination.
    6. Segregated areas are provided for the storage of rejected, recalled or returned materials or products.
    7. Highly active materials or products are stored in safe and secure areas.
    8. Printed packaging materials are considered critical to the conformity of the NHPs and special attention is paid to the safe and secure storage of these materials.

### Quality control area

* + 1. Quality control areas are designed to suit the operations to be carried out in them. There is sufficient space to avoid mix-ups and cross-contamination. There is adequate suitable storage space for samples and records.
    2. Normally, quality control areas are separated from production areas. It is particularly important for areas for the control of biological and micro-biologicals to be separated from each other. Special precautions may be needed in areas handling particular substances, such as biological samples.
    3. There are separate rooms to protect sensitive instruments from vibration, electrical interference, humidity and other factors.

### Ancillary areas

* + 1. Rest and refreshment rooms are separate from other areas. Facilities for changing clothes, for washing and toilet purposes are easily accessible and appropriate for the number of users. Toilets are not directly connected with production, testing or storage areas.
    2. Maintenance workshops are separated from production areas when possible. Whenever parts and tools are stored in the production area, they are kept in rooms or lockers reserved for that use.

## Equipment

Manufacturing equipment is:

* designed, located and maintained to suit its intended purpose
* designed so that it can be easily and thoroughly cleaned according to detailed and written procedures
* always stored in a clean and dry condition.

### General

* + 1. Repair and maintenance operations do not present any hazard to the quality of the products.
    2. Washing and cleaning equipment are chosen and used in a way that ensures it is not a source of contamination or damage.
    3. Equipment is installed in such a way as to prevent any risk of error or of contamination or damage.
    4. Production equipment does not present any hazard to the products. The parts of the production equipment that come into contact with the product are not reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

## Production

Production operations follow clearly defined procedures that ensure a product is of the requisite quality and are in accordance with the relevant manufacturing and product notifications.

Production is performed and supervised by competent people.

### General

* + 1. All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution is undertaken in accordance with written procedures or instructions and recorded if necessary.
    2. All incoming materials are checked to ensure that the consignment corresponds to the order. Containers are cleaned where necessary and labelled with the relevant information. Damage to containers and any other problem which might adversely affect the quality of a material are investigated and recorded. Incoming materials and finished products are physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.
    3. Intermediate and bulk products purchased as such are handled on receipt as though they were starting materials.
    4. All materials and products are stored under the appropriate conditions established by the manufacturer in a manner that permits batch segregation and stock rotation.
    5. Checks on yields, and reconciliation of quantities, are carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
    6. Operations on different products are only be carried out simultaneously or consecutively in the same room if there is no risk of mix-up or cross-contamination.
    7. At every stage of processing, products and materials are protected from microbial and other contamination.
    8. When working with dry materials and products, special precautions are taken to prevent the generation and spread of dust. This applies particularly to the handling of highly potent, reactive or sensitising materials.
    9. At all times during processing, all materials, bulk containers, major items of equipment and, if appropriate, the rooms used, are labelled or otherwise identified with an indication of the product or material being processed, its strength (if applicable) and batch number. If applicable, the stage of production is identified.
    10. Labels applied to containers, equipment or premises are 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).
    11. Checks are 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.
    12. Any deviation from instructions or procedures are avoided as far as possible. If a deviation occurs, it is approved in writing by a competent person, with the involvement of the Quality Function when appropriate.
    13. Access to production premises is restricted to authorised personnel.
    14. Normally, the production of products other than NHPs is avoided in the same areas and with the equipment destined for the production of NHPs.

### Prevention of cross-contamination in production

There are measures and procedures to prevent cross-contamination of a starting material or a product.

* + 1. The 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 the product being contaminated. Products in which contamination is likely to be most significant are those given in large doses and/or over a long time.
    2. Cross-contamination is avoided by appropriate technical or organisational measures, for example:
* production in segregated areas (required for products such as live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning
* providing appropriate air locks and air extraction
* minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air
* keeping protective clothing inside areas where products with special risk of cross-contamination are processed
* using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross- contamination
* using ‘closed systems’ of production
* testing for residues
* use of cleaning status labels on equipment.

### Validation

Validation studies are fit for purpose and confirm that manufacturing process and systems are properly developed.

* + 1. A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications.
    2. Validation studies reinforce GMP and are conducted in accordance with defined procedures. Results and conclusions are recorded.
    3. When any new manufacturing formula or method of preparation is adopted, steps are taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, is shown to yield a product consistently of the required quality.
    4. Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process are validated.
    5. Processes and procedures undergo periodic critical revalidation to ensure that they remain capable of achieving the intended results.
    6. Results and conclusions are recorded.

## Materials

### Purchase of materials

There are measures and procedures for the purchase of materials to ensure their quality.

* + 1. Materials are only purchased from approved suppliers named in the relevant specification and, if possible, directly from the producer.
    2. The purchase of starting materials is an important operation which involve staff who have a particular and thorough knowledge of the suppliers. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers.
    3. 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. Additional information relating to the various types of starting materials is provided in Section 5.

### Starting materials

There are measures and procedures for the handling and control of starting materials to ensure their quality.

* + 1. For each delivery, the containers are checked for integrity of package and seal, and for correspondence between the delivery note and the supplier’s labels. Starting material is traceable to the original manufacturer.
    2. There are 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 are identified. Only starting materials which have been released by the Quality Function and which are within their shelf-life are used.
    3. Starting materials are dispensed by designated people, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers. Each dispensed material and its weight or volume is independently checked and the check recorded. Materials dispensed for each batch are kept together and conspicuously labelled as such.
    4. If one material delivery is made up of different batches, each batch is considered as separate for sampling, testing and release.

### Processing operations – intermediate and bulk products

There are measures and procedures for the handling and control of intermediate and bulk products to ensure their quality.

* + 1. Before any processing operation is started, steps are taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.
    2. Intermediate and bulk products are kept under appropriate conditions.
    3. Critical processes are validated.
    4. Any necessary in-process controls and environmental controls are carried out and recorded.
    5. Any significant deviation from the expected yield is recorded and investigated.

### Packaging materials

There are measures and procedures for the handling and control of primary and printed packaging materials to ensure their quality.

* + 1. Each delivery or batch of printed or primary packaging material is given a specific reference number or identification mark.
    2. Particular attention is paid to printed materials. They are stored in adequately secure conditions so as to exclude unauthorised access. Cut labels and other loose printed materials are stored and transported in separate closed containers to avoid mix-ups. Packaging materials are issued for use only by authorised personnel following an approved and documented procedure.
    3. Outdated or obsolete primary packaging material or printed packaging material is destroyed and this disposal recorded.

### Packaging operations

Packaging operations minimise the risk of cross-contamination, misidentification and substitution of a product and packaging materials.

* + 1. When setting up a programme for the packaging operations, particular attention is given to minimising the risk of cross-contamination or mix-ups.
    2. Before beginning packaging operations, steps are 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 is performed according to an appropriate checklist.
    3. All products and packaging materials to be used are checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.
    4. Containers for filling are clean before filling. Attention is given to avoiding and removing any contaminants such as glass fragments and metal particles.
    5. Normally, filling and sealing is followed as quickly as possible by labelling. If it is not the case, appropriate procedures are applied to ensure that no mix-ups or mislabelling can occur.
    6. The correct performance of any printing operation (for example, code numbers and expiry dates) to be done separately or in the course of the packaging is checked and recorded. Attention is paid to hand-printed labels, which are re-checked at regular intervals.
    7. Special care is be taken when using cut labels and when overprinting is carried out off- the production line. Roll-feed labels are normally preferable to cut labels, in helping to avoid mix-ups.
    8. Checks are made to ensure that any electronic code readers, label counters or similar devices are operating correctly. Printed and embossed information on packaging materials are distinct and resistant to fading or erasing. On-line control of the product during packaging includes checking:
* the general appearance of the packages
* whether the packages are complete
* whether the correct products and packaging materials are used
* whether any overprinting is correct
* correct functioning of line monitors.
  + 1. Samples taken away from the packaging line are not returned.
    2. Products which have been involved in an unusual event are only reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed records are kept of this operation.
    3. Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced is investigated and satisfactorily accounted for before release.
    4. Upon completion of a packaging operation, any unused batch-coded packaging materials is destroyed and the destruction recorded. A documented procedure is followed if un-coded printed materials are returned to stock.

### Finished products

There are measures and procedures to ensure that a product is not released for sale or supply until its quality has been judged satisfactory.

* + 1. Finished products are held in quarantine until their final release under conditions established by the manufacturer.
    2. The evaluation of finished products and documentation which is necessary before release of product for sale is described in section 2.7 (Quality control). After release, finished products are stored as usable stock under conditions established by the manufacturer.

### Rejected, recovered and returned materials

There are measures and procedures to ensure that rejected materials and products are handled and disposed of appropriately.

* + 1. Rejected materials and products are clearly marked as such and stored separately in restricted areas. They are either be returned to the suppliers or, if appropriate, reprocessed or destroyed. Whatever action is taken is approved and recorded by authorised personnel.
    2. The reprocessing of rejected products is the exception. 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 is kept of the reprocessing.
    3. 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 a defined stage of manufacture is authorised beforehand. This recovery is carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery is recorded. The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, is considered by the Quality Function.
    4. Products returned from the market and which have left the control of the manufacturer are destroyed unless without doubt their quality is satisfactory; they may be considered for resale, re-labelling or recovery with a subsequent batch only after they have been critically assessed by the Quality Function 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 is taken into account in this assessment. If any doubt arises over the quality of the product, it is not considered suitable for reissue. Any action taken is recorded.

## Quality control

There are measures and procedures to ensure that materials are not released for use, nor a product released for sale or supply, until its quality has been judged satisfactory.

### Introduction

* + 1. Quality control is concerned with sampling, specifications and testing, documentation, and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory.
    2. Quality control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The independence of quality control from production is considered fundamental to the satisfactory operation of quality control.

### General

* + 1. Each holder of a manufacturing licence has an independent Quality Function. This department is independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control areas at their disposal. Adequate resources are available to ensure that all the quality control arrangements are effectively and reliably carried out.
    2. The principal duties of the person in charge of quality control are summarised in section 2.2. The person will also have other duties, such as to establish, validate 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 shelf-life claims for the products, and participate in the investigation of complaints related to the quality of the product. All these operations are carried out in accordance with written procedures and recorded if necessary.
    3. Finished product assessment embraces all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with finished product specification and examination of the final finished pack. Quality control personnel have access to production areas for sampling and investigation as appropriate.

### Good quality control laboratory practice

* + 1. Control laboratory premises and equipment meet the general and specific requirements for quality control areas given in section 2.8.
    2. The personnel, premises and equipment in the areas are appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside areas, in conformity with the principles detailed in section 4 (Contract analysis), can be accepted for particular reasons, and this is stated in the quality control records.

### Documentation

* + 1. Laboratory documentation follows the principles given in section 2.8.
    2. An important part of this documentation deals with quality control and the following details are readily available to the Quality Function:
* specifications
* sampling procedures
* testing procedures and records (including worksheets and/or laboratory notebooks)
* data from environmental monitoring, where required
* records of test methods, if applicable
* procedures for, and records of, the calibration of instruments and maintenance of equipment.
  + 1. Any quality control documentation relating to a batch record are retained for one year after the expiry date of the batch. For some kinds of data (such as tests results, yields and environmental controls) it is recommended that records are kept in a manner permitting trend evaluation. In addition to the information which is part of the batch record, other original data such as laboratory notebooks and/or records are retained and readily available.

### Sampling

Sample methods are fit for purpose to ensure the quality of the product.

* + 1. The sample taking is done in accordance with approved written procedures given in section 2.8.10.
    2. Reference samples from each batch of finished products are retained for one year after the expiry date. Reference samples of materials and products are of a size sufficient to permit at least a full re-examination.
    3. Samples of starting materials (other than solvents, gases and water) are retained for at least two years after the release of the product if their stability allows. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter.
    4. Finished products are kept in their final packaging and stored under the recommended conditions.

### Testing

Test methods are fit for purpose. Test results obtained are recorded and checked to ensure that they are consistent with each other.

* + 1. The tests performed are recorded, as set out in section 2.8.11.
    2. All the in-process controls, including those made in the production area by production personnel, are performed according to methods approved by quality control and the results recorded. Special attention is given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media. They are prepared in accordance with written procedures.
    3. Laboratory reagents intended for prolonged use are marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media is indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardisation and the last current factor is indicated.
    4. If necessary, the date of receipt of any substance used for testing operations (such as reagents and reference standards) is be indicated on the container. Instructions for use and storage are followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

### Ongoing stability programme

There is an ongoing stability programme to monitor the product over its shelf life to ensure the quality of the product.

* + 1. The purpose of an ongoing stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions. The extent of an ongoing stability programme relates directly to the risk that the product may pose to consumers.
    2. The protocol for an ongoing stability programme extends to the end of the shelf life period and includes the following parameters:
* number of batch(es) per strength and different batch sizes, if applicable
* relevant physical, chemical, microbiological and biological test methods
* acceptance criteria
* reference to test methods
* description of the container closure system(s)
* testing intervals (time points)
* description of the conditions of storage (standardised ICH conditions for long-term testing, consistent with the product labelling, are used)
* other applicable parameters specific to the NHP.

## Supporting documentation

### Introduction

The manufacturer’s documentation establishes, controls, monitors and records all activities that directly or indirectly impact on all aspects of the quality of the product.

* + 1. Good documentation is an essential part of quality assurance and is the key to operating in compliance with the principles of GMP. The various types of documents and media used are fully defined in the manufacturer’s quality assurance management system. Documentation may exist in a variety of forms, including paper-based, electronic or photographic media.
    2. The main objective of the system of documentation utilised must be to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of NHPs. The quality assurance management system includes sufficient instructional detail to facilitate a common understanding of the requirements, in addition to providing for sufficient recording of the various processes and evaluation of any observations, so that ongoing application of the requirements may be demonstrated.

### Site master file

* + 1. The site master files describes the GMP-principle related activities of the manufacturer.

### Material and product specifications

* + 1. The material and product specifications describe in detail the conformity requirements for the products or materials used or obtained during manufacture. They serve as a basis for quality evaluation.

### Starting and packaging materials

* + 1. Specifications for starting, primary or printed packaging materials include, or refer to, a description of the materials, including:
* the designated name (and the internal code reference, if applicable)
* the reference, if appropriate, to a pharmacopoeia and monograph
* the approved suppliers and the original producer of the material
* a specimen of printed materials
* directions for sampling and testing
* qualitative and quantitative requirements with acceptance limits
* storage conditions and precautions
* the maximum period of storage before re-examination.

### Intermediate and bulk products

* + 1. Specifications for intermediate and bulk products are available for critical steps, or if these are purchased or dispatched. The specifications are similar to specifications for starting materials or for finished products, as appropriate.

### Finished products

* + 1. Specifications for finished products include or refer to:
* the designated name of the product and the code reference if applicable
* the formula
* a description of the form of the product and package details
* directions for sampling and testing
* the qualitative and quantitative requirements, with the acceptance limits
* the storage conditions and any special handling precautions, if applicable
* the shelf life.

### Manufacturing, processing, packaging and batch processing instructions and records

#### Manufacturing formula and processing instructions

* + 1. The requirements for the manufacturing formula and the processing instructions may be combined into one document.
    2. The manufacturing formula includes:
* the name of the product, with a product reference code relating to its specification, if applicable
* a description of the form of the product, strength of the product and batch size
* a list describing all starting materials to be used, with the amount of each, including any substance that may disappear during processing
* a statement of the expected final yield with the acceptance limits, and of relevant intermediate yields, if applicable.
  + 1. The processing instructions includes:
* a statement of the processing location and the principal equipment to be used
* the methods, or reference to the methods, to be used for preparing the critical equipment (such as cleaning, assembling, calibrating, sterilising)
* 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
* detailed stepwise processing instructions (such as checks on materials, pre-treatments, sequence for adding materials, critical process parameters (for example, time, temperature))
* the instructions for any in-process controls with their limits
* if necessary, the requirements for bulk storage of the products, including the container, labelling and special storage conditions if applicable
* any special precautions to be observed.

#### Packaging instructions

* + 1. The packaging instructions and batch processing record may be combined into one document.
    2. Approved packaging instructions for each product, pack size and type exist and include or refer to:
* the name of the product, including the batch number of bulk and finished product
* a description of its form, and strength if applicable
* the pack size expressed in terms of the number, weight or volume of the product in the final container
* a complete list of all the packaging materials required, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material
* if 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
* checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations (line clearance), and that equipment is clean and suitable for use
* special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin
* a description of the packaging operation, including any significant subsidiary operations, and equipment to be used
* details of in-process controls with instructions for sampling and acceptance limits.

#### Batch processing record

* + 1. A batch processing record is kept for each batch processed. It is based on the relevant parts of the manufacturing formula and processing instructions, and contain:
* the name and batch number of the product
* dates and times of commencement, of significant intermediate stages and of completion of production
* identification (such as initials) of the operator(s) who performed each significant step of the process and, if appropriate, the name of any person who checked these operations
* the batch number and/or unique identifier number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added)
* any relevant processing operation or event and major equipment used
* a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained
* the product yield obtained at different and pertinent stages of manufacture, as appropriate
* notes on special problems including details, with signed authorisation for any deviation from the manufacturing formula and processing instructions
* approval by the person responsible for the processing operations.

### Procedures and records

* + 1. Standard operating procedures give direction for performing certain operations. These need only be simple in format and content for smaller manufacturers.
    2. Records provide evidence of various actions taken to demonstrate compliance with instructions, such as activities, events and investigations, and in the case of manufacturer’s batches, a history of each batch of product, including its distribution. Records include the raw data which is used to generate other records. For electronic records users define which data are to be used as raw data, that being data on which quality decisions are based.

### Receipt

* + 1. There are written procedures and records for the receipt of each delivery of each starting material (including bulk, intermediate or finished goods), primary, secondary and printed packaging materials.
    2. The records of the receipts include:
* the name of the material on the delivery note and the containers
* the ‘in-house’ name and/or code of material (if different from above)
* date of receipt
* supplier’s name and manufacturer’s name
* manufacturer’s batch or reference number
* total quantity and number of containers received
* the batch number assigned after receipt
* any relevant comment.
  + 1. There are written procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

### Sampling

* + 1. There are written procedures for sampling, which describe:
* the method of sampling
* the equipment to be used
* the amount of the sample to be taken
* instructions for any required subdivision of the sample
* the type and condition of the sample container to be used
* the identification of containers sampled
* any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials
* the storage conditions
* instructions for the cleaning and storage of sampling equipment.

### Testing

* + 1. There are written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used.
    2. The tests performed are recorded and the records include at least:
* the name of the material or product and, if applicable, dosage form
* the batch number and, if appropriate, the manufacturer and/or supplier
* references to the relevant specifications and testing procedures
* test results, including observations and calculations, and reference to any certificates of analysis
* dates of testing
* the initials of the people who performed the testing
* the initials of the people who verified the testing and the calculations, if appropriate
* a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

### Other activities

* + 1. Written release and rejection procedures are available for materials and products, and in particular for release of the finished product.
    2. A system is in place to indicate special observations and any changes to critical data. Records are maintained for the distribution of each batch of a product in order to facilitate recall of any batch, if necessary.
    3. There are written procedures and associated records of actions taken or conclusions reached, if appropriate, for:
* validation and qualification of processes, equipment and systems
* equipment assembly and calibration
* maintenance, cleaning and sanitation
* personnel matters including signature lists, training in the principles of GMP and technical matters, clothing and hygiene, and verification of the effectiveness of training
* environmental monitoring
* pest control
* complaints
* recalls
* returns
* change control
* investigations into deviations and non-conformances
* internal quality/compliance audits
* supplier audits.
  + 1. Clear operating procedures are available for major items of manufacturing and test equipment. An inventory of documents within the quality assurance management system is maintained.

### Retention of documents

* + 1. It is clearly defined which record is related to each manufacturing activity and where this record is located. Secure controls are in place to ensure the integrity of the record throughout the retention period and validated where appropriate. Specific requirements apply to batch documentation, which must be kept for one year after expiry of the batch to which it relates, or at least five years after certification of the batch, whichever is longer.

### Production and quality control documentation

* + 1. All document types are defined and adhered to. The requirements apply equally to all forms of document media types. Complex systems need to be understood, well documented and validated, and adequate controls are in place. Many documents (instructions and/or records) may exist in hybrid forms, with some elements electronic and others on paper. Relationships and control measures for master documents, official copies, data handling and records are stated for both single and hybrid systems. Appropriate controls for electronic documents such as templates, forms, and master documents are implemented. Appropriate controls are in place to ensure the integrity of the record throughout the retention period.
    2. Documents are designed, prepared, reviewed and distributed with care.
    3. The reproduction of working documents from master documents do not allow any error to be introduced through the reproduction process.
    4. Documents containing instructions are approved, signed and dated by appropriate and authorised persons. Documents have unambiguous contents and be uniquely identifiable. The effective date is defined.
    5. Documents containing instructions are laid out in an orderly fashion and are easy to check. The style and language of documents fit with their intended use. Standard operating procedures, work instructions and methods are written in an imperative mandatory style.
    6. Documents within the quality assurance management system are regularly reviewed and kept up to date. When a document has been revised, systems are operated to prevent inadvertent use of superseded documents.
    7. Documents are not handwritten, although if documents require the entry of data, sufficient space is provided for such entries.

### Good documentation practices

* + 1. Handwritten entries in records are made in clear, legible, indelible way. Records are made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of NHPs are traceable. Any alteration made to the entry on a document is signed and dated; the alteration permits the reading of the original information. If appropriate, the reason for the alteration is recorded.

# Complaints and recalls

## Complaints

There are measures and procedures to manage the investigation of complaints about a product.

When manufacturers of NHPs receive complaints about defects associated with their products they must conduct an investigation to determine the basis for the complaint.

Recalls must only be conducted with the prior knowledge of the Authority. The Authority must be informed if a manufacturer is considering action following possible faulty manufacture, product deterioration, or any other serious quality problems with a product.

### General

* + 1. The investigation is conducted in line with existing written policies and procedures that have been developed specifically for the purpose of conducting an investigation.
    2. A policy and process for conducting a product recall to remove all defective products from the market as soon as possible is described, and followed if required.

### Designated person

* + 1. There is a ‘designated person’ in the organisation responsible for handling and investigating complaints. This is also the individual who, together with other staff as appropriate, will make decisions about the remedial actions that the manufacturer will take following the investigation.

### Documentation

* + 1. There are written policies and procedures describing responses or remedial actions to be taken for complaints.
    2. Records will be kept for every complaint received, together with the outcomes of the investigation into the complaint.

### Processes

* + 1. If a product defect is discovered or suspected in a batch, the manufacturer will check other batches in order to determine whether they are also affected. In particular, if a batch has been reworked and incorporated into other batches, these batches that contain reworks of the defective batch are investigated.
    2. All the decisions and measures taken as a result of a complaint are recorded and referenced back to the corresponding batch records.
    3. Complaints records are reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.

## Recalls

There are measures and procedures to manage the recall of a product.

Recalls must be able to be initiated promptly and at any time.

Recalls must only be conducted with the prior knowledge of the Authority.

### Designated person

* + 1. There is a ‘designated person’ responsible for handling and coordinating all recalls. This is also the individual who, together with other staff as appropriate, will make decisions about the actions that the manufacturer will take to carry out the recall.

### Documentation

* + 1. There are written policies and procedures describing how to conduct a product recall.
    2. There are records kept for every recall undertaken.
    3. The recall policies and procedures are regularly checked and updated when necessary, in order to organise any recall activity.

### Processes

* + 1. The manufacturer will ensure that distribution records are available that detail 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 samples.
    2. Recalled and returned products are identified and stored separately in a secure area. The progress of the recall process is documented and a report detailing the final status of the product and the recall issued. The report includes data that reconciles the amount of product recalled.
    3. The manufacturer regularly evaluates the effectiveness of the arrangements for recalls, and update the accompanying policies and procedures.

# Contract manufacture and analysis

## Introduction

Arrangements for contract manufacture and analysis of products are clearly defined and documented.

* + 1. Contract manufacture and contract analysis (or contract testing) is defined as the manufacture (or partial manufacture) and/or analysis of a product to the order of one person or organisation (the contract giver) by another independent person or organisation (the contract acceptor). Contract manufacture or analysis is considered as an extension of the contract giver’s operations.

## Contract – general considerations

* + 1. There is a written contract that details the definition of the contract roles performed, and the obligations with respect to documentation, product quality control, release of batches of product, and the responsibilities around investigation of any potential defects.
    2. There is a written contract covering the contract manufacture and/or testing arrangements made. All arrangements for contract manufacture and/or testing (including any proposed changes in technical or other arrangements) is in accordance with the product notification for the product concerned. A contract is drawn up between the contract giver and the contract acceptor which specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the contract are drawn up by competent persons suitably knowledgeable in relevant aspects of the product, their testing and the principles of GMP.
    3. The contract describes 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 testing.
    4. Manufacturing, analytical and distribution records, and reference samples are 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 are accessible and specified in the defect/recall procedures of the contract giver. The contract permits the contract giver to visit and audit the facilities of the contract acceptor.
    5. In the case of contract testing, the contract states whether the samples will be provided by the contract giver or the contract acceptor will take samples at the premises of the manufacturer.
    6. In the case of contract testing, the contracted testing facility understands that it is subject to inspection by the Authority, or another auditing body authorised on its behalf.

## Contract giver obligations

* + 1. The contract giver is the party responsible for assessing the competence of the contract manufacturer and/or tester to carry out the work required and for ensuring the principles outlined in this Code are followed.
    2. The contract giver provides the contract acceptor with all information necessary to carry out the contracted operations correctly in accordance with the product notification and any other legal requirements.
    3. The contract giver ensures that the contract acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to their premises, equipment, personnel, other materials or other product.
    4. The contract giver ensures that all processed products and materials delivered to them by the contract acceptor comply with their specifications or that the products have been released by an authorised person.

## Contract acceptor obligations

* + 1. The contract acceptor has adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the contract giver.
    2. The contract acceptor ensure that all products or materials delivered to them are suitable for their intended purpose.
    3. The contract acceptor does not pass to a third party any of the work entrusted to them under the contract without the contract giver’s prior evaluation and approval of the arrangements.
    4. Arrangements made between the contract acceptor and any third party ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract acceptor.
    5. The contract acceptor refrains from any activity which may adversely affect the quality of the product manufactured and/or analysed for the contract giver.

# Starting material requirements

## Starting materials of herbal origin

There are measures and procedures to ensure that starting herbal material is of an acceptable quality.

### Introduction

* + 1. For the purposes of this section, the term herbal origin includes plant, algae, fungi and lichens, and exudates. The use of the terms plant, herbal, substance, preparation or product are used correspondingly.
    2. Herbal material is complex and variable in nature. As herbal material can be used in its native state, as prepared or processed material, or as substances obtained through extraction or other physical or chemical transformations, the control of starting material, storage and processing are particularly important.

### Supply of starting material

* + 1. If obtained from an outside supplier (third party), there is adequate supporting data to persuade the manufacturer that the material is suitable for use, particularly as examples abound of adulteration of plant material with toxic herbs or drugs.

### Growing, collection and identification

* + 1. Manufacturers verify that producers/processors/suppliers of herbal materials are real, and ensure that there is adequate audit of outside producers, particularly whether the producer complies with good agricultural and collection practice.
    2. Guidance documents relating to herbal material that will be accepted for this part of the Code are listed in section 7.

### Specifications and tests

* + 1. Specifications for starting materials include, if relevant:
* binomial scientific name of the plant (genus, species, subspecies, author, cultivar)
* details of the source: country or region of origin
* cultivation details: time of harvesting, collection procedures, possible pesticides used (if applicable)
* parts of the plant used
* drying system
* description of the material (macro and microscopic)
* suitable identity tests
* water content (as determined according to the relevant pharmacopoeia)
* tests for microbial or fungal contamination
* tests for toxic metals
* tests for foreign material
* any other tests required by the relevant pharmacopoeia
* any treatments to reduce contamination or infestation (which may include tests for residues and limits).
  + 1. All other aspects of the Code apply to starting materials of herbal origin (if applicable).

## Starting materials of animal origin

If final product manufacturers use animal materials or ingredients in their products, there is adequate evidence that their source is TSE free.

* + 1. For the purposes of this section, the term animal includes both vertebrates and invertebrates, and diverse groups such as molluscs, arthropods, annelids, sponges and jellyfish, and bacteria and viruses.

### Transmissible spongiform encephalopathy status

* + 1. For materials derived from animals that may harbour transmissible spongiform encephalopathy (TSE), adequate measures are taken to ensure that these materials or ingredients (such as gelatine, magnesium or calcium stearate, stearic acid) used in the product are free from viral or TSE contamination.
    2. For some sources of materials, a European Pharmacopoeia Commission certificate of suitability is acceptable as evidence of freedom from TSE agents (see: [www.edqm.eu/en/edqm-homepage-628.html](http://www.edqm.eu/en/edqm-homepage-628.html)). Alternatively, certification from a national authority such as a Department of Agriculture or a veterinarian that the material is free from TSE agents would also be acceptable evidence.

### Specifications and tests

* + 1. Specifications for starting materials include, if relevant:
* binomial scientific name of the animal (genus, species, subspecies, author)
* details of the source (country or region of origin)
* parts of the animal used
* tests for foreign material
* any other relevant tests required by the relevant pharmacopoeia
* any treatments to reduce contamination or infestation.
  + 1. All other aspects of the Code apply to starting materials of animal origin (if applicable).

# Dose form requirements

If particular dose forms are manufactured, specific testing requirements are included in the specifications, as applicable.

### Ear preparations

Uniformity of mass

### Topical products

Microbial testing

Preservative efficacy (if preservatives are used in the formulation)

Uniformity of mass (powders)

Release of active substance (patches)

### Granules

Disintegration

Dissolution

Uniformity of dosage unit (granules for single dose use)

### Modified release granules

Release of active substance

### Chewing gum

Uniformity of mass

### Nasal preparations

Uniformity of delivered dose (if applicable)

Uniformity of mass

### Oromucosal preparations

**(including lozenges, pastilles, buccal and sublingual tablets, troches)**

Uniformity of mass

Dissolution (where appropriate)

### Oral liquids

**(including suspensions, emulsions and syrups)**

Microbial testing

Preservative efficacy (if preservatives are used in the formulation)

Uniformity of mass or homogeneity of suspension

Uniformity of content if the dose contains 2 mg or less of the active ingredient

### Oral tablets, capsules, pills and powders

Disintegration

Dissolution (if appropriate)

Uniformity of mass or uniformity of dose (if appropriate)

Microbial testing (powders)

### Oral modified release solid dose forms

Release of active substance

### Suppositories

Disintegration

Release of active substance

### Pessaries

Uniformity of mass

Release of active substance

# Standards and guidelines

### Agricultural and Collection Practices

WHO Good Agricultural and Collection Practices (GACP) for medicinal plants

<http://apps.who.int/medicinedocs/en/d/Js4928e/>

European Medicines Agency. HPMC Guideline on GACP. Doc. Ref. EMEA/HMPC/246816/2005

[www.ema.europa.eu/ema/index.jsp?curl=search.jsp&q=Doc.+Ref.+EMEA%2FHMPC%2F246816%2F2005&btnG=Search&mid](http://www.ema.europa.eu/ema/index.jsp?curl=search.jsp&q=Doc.+Ref.+EMEA%2FHMPC%2F246816%2F2005&btnG=Search&mid)=

European Herb Growers Association – Guidelines for Good Agricultural and Wild Collection Practice (GACP) of Medicinal and Aromatic Plants

[www.europam.net/documents/gacp/EUROPAM\_GACP\_7.3.pdf](http://www.europam.net/documents/gacp/EUROPAM_GACP_7.3.pdf)

AHPA-AHP Good Agricultural and Collection Practice for Herbal Raw Materials

American Herbal Products Association-American Herbal Pharmacopoeia

[www.ahpa.org/Default.aspx?tabid=219](http://www.ahpa.org/Default.aspx?tabid=219)

WHO guidelines on good manufacturing practices (GMP) for herbal medicines

<http://apps.who.int/medicinedocs/en/m/abstract/Js14215e/>

**Standards**

AS/NZS ISO 31000:2009

ISO9001 series on quality management

### FDA Guidance

Part 111 – Current Good Manufacturing in Manufacturing, Packaging, Labelling, or Holding Operations for Dietary Supplements

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=111

### Pharmaceutical Inspection Convention (PIC/S) (Pharmaceutical Inspection Co-operation Scheme)

General Guidance on Good Manufacturing Practice (GMP) requirements and other useful guidance documentation, including:

* PIC/S GMP guide (part I: basic requirements for medicinal products)
* PIC/S GMP guide (part II: basic requirements for active pharmaceutical ingredients) PIC/S GMP guide (annexes)

[www.picscheme.org/publication.php](http://www.picscheme.org/publication.php)

### International Conference on Harmonisation

ICH Q7 – Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

www.ich.org/products/guidelines/quality/quality-single/article/good-manufacturing-practice-guide-for-active-pharmaceutical-ingredients.html

### Pharmacopoeia and Monographs

American Herbal Pharmacopoeia

Ayurvedic Pharmacopoeia

British Pharmacopoeia

British Herbal Pharmacopoeia

European Pharmacopoeia

European Scientific Cooperative on Phytomedicine (ESCOP)

German Commission E Monographs

Indian Herbal Pharmacopoeia

Pharmacopoeia of the People’s Republic of China

United States Pharmacopoeia and National Formulary

World Health Organization Monographs on Selected Medicinal Plants

### Transmissible Spongiform Encephalopathies

ICH Q6B – Specifications: Test procedures and acceptance criteria for biotechnological / biological products

[www.ich.org/products/guidelines/quality/article/quality-guidelines.html](http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html)

Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3)

[www.ema.europa.eu/docs/en\_GB/document\_library/Scientific\_guideline/2009/09/WC500003700.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003700.pdf)

Guidance for Industry: Revised preventive measures to reduce the risk of transmission of Creutzfeldt-Jakob disease (CJD) and new variant Creutzfeldt-Jakob disease (nvCJD) by blood and blood products.

[www.fda.gov/downloads/%20BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM213415.pdf](http://www.fda.gov/downloads/%20BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM213415.pdf)