Global Guide to

Good Manufacturing Practice for Supplements

IADSA

International Alliance of Dietary/
Food Supplement Associations

The International Alliance of Dietary/Food Supplement Associations (IADSA) brings together over 50 associations of dietary/food supplement manufacturers and distributors from across the world. IADSA's central goal is to ensure a greater exchange of information about the science and regulation of dietary supplements and ingredients across government, industry and the scientific community.

The Global Guide to Good Manufacturing Practice for Supplements has been developed by a team of technical and regulatory experts from across the world with specialist knowledge in supplement manufacturing. It is designed to provide clear guidance in a non-prescriptive framework format that will allow for flexibility in application within any country or region. Its aim is to help raise the standard of all supplements produced around the globe to the level of quality and safety expected by consumers and regulators alike.

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Section 1

Introduction

Broadly defined, a Supplement is a product that is intended to supplement the normal diet with a concentrated source of nutrient(s) and/or other substance(s). Generally, a supplement is sold in a controlled dosage form for oral intake such as a liquid, powder, tablet, capsule, pastille or other such similar forms. Definitions for supplements that are currently in use globally in the major economic areas are listed in Annex IV.

Supplements have to comply with all relevant aspects of legislation in their country of production and sale in terms of composition, manufacture and control.

As supplements are designed to supply nutrients, micronutrients and other physiologically active substances in predetermined amounts, the greater proportion of products are manufactured using specialised skills and equipment.

This document is intended to provide guidelines for the promotion of best practice in the production (manufacturing, quality control, packaging, distribution and storage) of supplements.

Where applicable, these guidelines apply equally to supplement companies who have their products contract manufactured and also to those who are solely distributors of products.

Manufacturers and distributors of supplements should comply with all relevant national legislation in their home country and also that of any countries to which they export their products.

Section 2

Quality management

2.1 General principle

As a general principle, Quality Management is defined as co-ordinated activities to direct and control an organisation with regard to quality. There should be a comprehensive system so designed, documented, implemented and controlled, and so furnished with personnel, equipment and other resources, as to provide assurance that products will be consistently fit for their intended use. The attainment of this quality objective requires the involvement and commitment of all concerned, at all stages of manufacture, storage and distribution.

The concept of 'quality by design' is important for Quality Management. This means that the product should be designed and developed in a way that takes into account all the essential quality requirements.

The quality objective shall be achieved by an integrated system including Quality Assurance, Quality Control and Good Practice. These three aspects of quality are defined as follows:

2.2 Good practice for production

The basic requirements of Good Practice are that:

a) all manufacturing processes should be clearly defined, and known to be capable of achieving the desired ends;

b) all necessary resources and facilities are provided, including:

- appropriately trained personnel;
- adequate premises and space;
- suitable equipment and services;
- correct materials, containers and labels;
- approved procedures (including cleaning procedures);
- suitable storage and transport;

c) operators are trained to carry out the procedures correctly.

2.3 Quality assurance

Quality Assurance is the part of Quality Management focusing on increasing the ability to fulfil quality requirements. The objectives of Quality Assurance are achieved when processes have been defined which, when followed, will yield a product that complies with its specification and the quality expected, and when the finished product:

a) contains the correct ingredients in the correct proportions;

b) has been correctly processed, according to the defined procedures;

c) is of the purity required;

d) is enclosed in its proper container, which;

e) bears the correct label (or is otherwise suitably marked or identified);

f) is stored, distributed and recommendations given for its subsequent handling in accordance with the recommended storage conditions, so that its quality is maintained throughout its designated or expected life.

Quality Assurance normally covers the following points:

a) procedures are written in instructional form, in clear and unambiguous language, and are specifically applicable to the facilities provided;

b) records are made during manufacture (including packaging), which demonstrate that all the steps required by the defined procedures were in fact taken, and that the quantity and quality produced were those expected;

c) records of manufacture and distribution, which enable the complete history of a lot (batch) to be traced, are retained in a legible and accessible form;

d) a system is available to withdraw or recall from sale or supply any lot or product, should that become necessary;

e) the Quality Assurance procedures of the suppliers of raw and packaging materials should be monitored, preferably with regular audits. A Supplier Quality Assurance procedure should be developed to define the criteria for selection, approval, review and ongoing approval to ensure that purchased products and services meet the organisation's requirements (see Annex V);

f) there needs to be rapid feedback of information in the form of summaries of quality performance data (accompanied, where appropriate, by advice) to manufacturing personnel, enabling prompt adjustment or corrective action to be taken when necessary; and to the purchasing function in respect of raw material lots;

g) customer/consumer complaint samples should be examined, the causes of defects investigated where possible, and appropriate measures advised for corrective action to prevent recurrence (see Chapter 11);

h) due heed should be taken of new developments in relevant legislation, especially those requiring changes in compositional standards and labelling requirements which may necessitate changes to specifications for raw materials or finished products.

A continual review of the Quality Assurance systems should be undertaken to ensure that they remain effective. This should be done by self-inspections and/or third party audits.

2.4 Quality control

Quality Control is the obligation to have in place an effective monitoring system that verifies compliance with specified requirements and parameters, and defines suitable corrective action in the event of non-compliance. As with Quality Assurance, Quality Control must be an ongoing process to ensure that quality of the product is maintained.

To achieve effective control of quality:

a) the authority and responsibilities of the Production Management and the Quality Control Management functions respectively should be clearly defined so that there is no misunderstanding. Where possible, the Quality Control Management should be on a separate reporting structure from the Production Management and be empowered to make independent decisions on the product quality;

b) adequate facilities and staff should be available for sampling, inspecting and testing starting materials, packaging materials, intermediate, bulk and finished products, and where appropriate, for determining environmental quality;

c) samples of starting materials, packaging materials, intermediate products, bulk products and finished products should only be taken by authorised personnel and using methods approved by the person responsible for Quality Control;

d) results of the inspection and testing of materials, and of intermediate, bulk or finished products, should be formally assessed against specification by the person responsible for Quality Control (or a person designated by him) before products are released for sale or supply;

e) product assessment should include a review and evaluation of relevant manufacturing (including packaging) documentation;

f) sufficient reference samples of starting materials and finished products should be retained (the latter in the final pack for the finished product) to permit future examination if necessary.

See also chapter 13.

Section 3

Premises and equipment

3.1 General

Buildings should be located, designed, constructed, adapted and maintained to suit the operations carried out in them and to facilitate the protection of materials and products from contamination or deterioration. Equipment should be designed, constructed, adapted, located and maintained to suit the processes and products for which it is used and to facilitate protection of the materials handled from contamination or deterioration.

3.2 General requirements for premises

a) Premises must be designed to allow cleaning and maintenance to be carried out to a high level.

b) Layout, design, construction and size should be such as to:

- permit hygienic cleaning, good hygiene practices, and suitable temperature/humidity conditions where necessary;
- prevent cross contamination in the premises and contamination from external sources such as pests.

c) Facilities that must be provided:

- availability of washbasins, lavatories;
- adequate supply of potable water;
- ventilation;
- lighting;
- drainage facilities;
- changing facilities for staff.

3.3 General requirements in rooms where supplements are prepared, treated, or processed

a) Construction and design. The following surfaces and fittings must be smooth, crevice-free and easily cleanable:

- floor surfaces;
- wall surfaces;
- ceilings and overhead fixtures;
- windows;
- doors;
- surfaces in contact with raw materials, intermediate product or finished product.

b) Facilities. Adequate facilities must be provided for cleaning tools and equipment where necessary.

3.4 Premises

3.4.1 General premises and buildings

Premises should:

- provide sufficient space to suit the operations to be carried out;
- allow an efficient flow of work;
- provide suitable internal storage areas;
- facilitate effective communication and supervision;
- be sited with due regard for the provision of services needed and to avoid contamination from adjacent activities. In existing premises, effective measures should be taken to avoid such contamination;
- be maintained in a good state of repair. The condition of buildings should be reviewed regularly, and repairs effected where necessary. Special care should be exercised to ensure that building materials of construction, repair or maintenance operations are not allowed to affect adversely product quality or integrity;
- be constructed and maintained with the object of protecting against the entrance and harbouring of vermin, birds, insects, other pests and pets;
- be maintained in a clean and tidy condition (including processing areas, laboratories, stores, passageways and external surroundings).

Manufacturing areas should not be used as a general right of way for personnel or materials, or for storage (except of materials in process).

3.4.2 Ventilation and lighting

Buildings should be effectively lit and ventilated, with appropriate air control facilities (including temperature, humidity and filtration where necessary) suitable both to the operations undertaken within them and to the external environment. Air supply and extraction trunking should be designed so that contaminants are not introduced into products. All lighting appliances should be completely covered by shatterproof plastic diffusers or sleeve covers or, if this is not possible, by a fine metal mesh screen, to contain any pieces of glass in the event of shattering. Procedures should be developed detailing the action to be taken in the event of any breakage or damage to glass, ceramic or hard plastic items.

Fans should be positioned in order to avoid contamination hazards caused by either intake of noxious vapours, gases or solids, or release of materials which could contaminate the product, and with due regard for the local environment and the avoidance of nuisance such as odour, noise or dust emissions.

Pipework, light fittings, ventilation points and other services in manufacturing areas should be sited to avoid creating recesses which are difficult to clean. Services should preferably run outside the processing areas. They should be sealed into any walls and partitions through which they pass.

Working conditions (e.g. temperature, humidity, noise levels) should be such that there is no adverse effect on the product, either directly or indirectly, via the operator.

3.4.3 Floors, walls and ceilings

Floors in manufacturing areas should be made of impervious materials, laid to an even surface and free from cracks and open joints in areas where product is exposed. They should be of adequate construction and material for the wear and tear and conditions of manufacture encountered.

Drains should be of adequate size, and should have trapped gullies and proper ventilation. Any open channels should be shallow to facilitate cleaning.

Walls should be sound and finished with a smooth impervious and easily cleaned surface.

Windows should be of toughened glass or plastic, adequately screened and secured, and with ledges sloped away from the glass at an angle to prevent items being left on them. Materials should be chosen so as to avoid tainting or otherwise contaminating the product.

Doors should have smooth and non-absorbent surfaces in order that they are easy to clean and, when necessary, disinfect.

Ceilings should be so constructed and finished that they can be maintained in a clean condition. Suspended ceilings should not permit the accumulation of dirt and should be so installed as to reduce condensation, the formation of mould and the release of loose particles.

The coving of junctions between walls, floors and ceilings in critical areas is recommended.

3.4.4 Cleaning and waste

All operations should be carried out in such a way that the risk of contamination of one product or material by another is minimised.

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 of at regular and frequent intervals. Disposal of printed packaging materials or raw materials and rejected products should be carefully controlled.

There should be written cleaning procedures and schedules for manufacturing and storage areas, external areas and vehicles used in the distribution supply chain. A Site Hygiene Plan should be developed to ensure a hygienic manufacturing site, thus minimising the risk of potential product contamination. This plan should be regularly reviewed.

Vacuum or wet cleaning methods are to be preferred. Compressed air, hoses, pressure cleaners, brooms and brushes should be used with care, so as not to incur the risk of product contamination.

Products used for cleaning and disinfecting purposes should be appropriate for their required function and should be stored in a location which is separate from the processing areas.

3.4.5 Receiving and despatch areas

Protection from the weather should be provided for receiving and despatch areas, and for materials or product in transit.

Where appropriate, a defined deboxing/debagging area should be provided for those raw materials or packaging materials which arrive in external packaging.

3.4.6 Personnel hygiene facilities

Cloakrooms or changing rooms should be provided and be separate from, or partitioned from, manufacturing areas.

Provision should be made for separate accommodation for clothing and footwear not being worn during working hours.

Adequate sanitary conveniences (flush toilets) must be provided and kept clean, and should include notices instructing users to wash their hands after using the convenience. Toilets must not open directly to manufacturing areas.

Rest and refreshment rooms should be separate from other areas.

Hand-wash basins and accompanying facilities (hot and cold water or temperature controlled hot water, soap or detergent, nail brushes and clean towels or other suitable drying facilities) must be provided and kept clean, at convenient places accessible to personnel.

First aid materials should be provided in a place readily accessible to authorised First Aiders.

3.4.7 Pest control

There should be either trained personnel to oversee infestation control or a professional infestation control company should be employed for regular inspection, advice and treatment if required. Procedures for pest control should be commensurate with the local habitat and risks.

Useful general information on pest control can be found in the Codex General Principles (see Annex V).

3.5 Equipment

Equipment should be so designed and arranged as to protect the contents from external contamination and should not endanger a product through contamination from leaking joints/glands, lubricant drips and the like, or through inappropriate modifications or adaptations.

3.5.1 Surfaces and materials in contact with supplements

All surfaces and materials in contact with supplements:

- should be inert to the supplements under the conditions of use and should not yield substances which might migrate or be absorbed into the supplements;
- should be microbiologically cleanable, smooth and non-porous so that particles are not caught in surface crevices and become difficult to dislodge;
- should be visible for inspection or the equipment should be easily dismantled for inspection, or it should be demonstrated that routine cleaning procedures eliminate the possibility of contamination.

All surfaces in contact with supplements should be readily accessible for manual cleaning or, if not readily accessible, then easily dismantled for manual cleaning, or if clean-in-place techniques are used, it should be demonstrated that the results achieved without disassembly are the equivalent of those obtained with disassembly and manual cleaning.

All interior surfaces in contact with supplements should be so arranged that the equipment is self-emptying or self-draining.

Exterior surfaces of equipment not in contact with supplements should be so arranged to prevent harbouring of soils, micro-organisms or pests in and on the equipment, floors, walls and supports.

There should be detailed written instructions for cleaning and sanitising. Specified materials, methods, safety precautions and suitable facilities should be provided.

3.5.2 Plant and equipment

Plant and equipment should be cleaned and serviced immediately after use. Any faults should be recorded.

Any missing components such as nuts, springs, clips, etc. should be reported immediately. All lots produced since the previous check should be quarantined until the missing item is found or the lots have been shown to be clear (e.g. by metal detection or sieving).

Procedures describing the action to be taken for the control of foreign body contamination should be formally documented, and personnel should be actively encouraged to report without delay any incident of contamination or potential contamination of the product.

Plant and equipment should be checked for cleanliness and integrity before every use and to this end should be designed with sound, secure, quick-release systems for inspection and disassembly.

Appropriate precautions for ventilating fumes from power driven equipment, heaters etc. should be taken.

Preventive maintenance should be considered for all equipment and components. A maintenance procedure, based upon risk assessment, should be established covering both preventive and responsive maintenance. This procedure must be highlighted to maintenance and machine servicing contractors.

Regular calibration of all measuring equipment (weight, volume, temperature, etc.) should be carried out using suitable standards. Detailed records of the calibrations should be maintained and routinely audited to ensure that all calibration is up to date and that the equipment is working to the required level of accuracy. Once a piece of equipment has been calibrated it should only be adjusted by authorised personnel according to prescribed procedures, with any adjustments being formally recorded.

Cold storage equipment should be fitted with a temperature-measuring device that indicates the temperature within the storage compartment. The temperature should be recorded either manually or automatically at regular intervals and the equipment should be fitted with an alarm system that gives an alert if there is a significant change in temperature.

Procedures should be in place to ensure that all product produced since the last satisfactory check can be identified, isolated and retested should the inspection and testing equipment be found to be functioning incorrectly.

Only potable water should be used as a minimum standard for all uses in production. Higher standards (such as de-ionised water) may be required for certain operations. In locations where a potable water supply is not standard supply, documentation should be obtained and retained that confirms the water used in production is of at least the minimum standard required.

Section 4

Personnel and training

4.1 General

Compatible with the size and type of business there should be sufficient personnel at all levels with the ability, training, experience and, where necessary, the professional and technical qualifications, appropriate to the tasks assigned to them. Their duties and responsibilities should be clearly explained and recorded as job descriptions or by other suitable means. Formally authorised and documented deputies/delegates should be assigned to cover the absence of key personnel.

4.2 Training

Training should cover not only specific tasks, but best practice generally, and the importance of, and factors involved in, personal hygiene. Training should be given to each new employee upon employment and then repeated, revised and enhanced as applicable, with consideration given to any language or literacy difficulties. Refresher training should be given particularly in the case of poor hygiene practices being identified.

In addition to the training of employees involved in production, quality assurance and quality control, appropriate training should be given to all those who have any contact with the manufacturing areas or activities, such as office, maintenance and cleaning staff as appropriate.

Persons* involved in the training of supplement handlers and in the administration of internal and external audits should be trained to a nationally recognised standard where applicable.

Training should be planned and recorded for each individual employee.

*Persons - in this context allows personnel or external consultants to be used.

4.3 The training of supplement handlers

Businesses should ensure that supplement handlers are supervised and instructed and/or trained in hygiene matters commensurate with their work activity.

Supplement businesses should identify the detailed measures necessary and relevant to their own operation. These measures should ensure that all potential supplement handlers, including supervisors and managers, have the knowledge necessary for them to play their part in handling the product hygienically so that the health of the consumer is properly safeguarded. What is appropriate in one business may not necessarily be appropriate in another.

For example:

- some businesses have a high turnover of casual labour making formal training difficult, but making good instruction and supervision very important;
- the nature and type of supervision necessary will depend on the number of supplement handlers within the unit of the business and the nature of their work.

The supervision and instruction and/or training needs must relate to the work undertaken by supplement handlers themselves and those in the nearby environment and the risks to product safety presented by their activities. In deciding on the relative risks presented, businesses should consider:

a) The nature of the supplements with which the operators work, for example, supplements in capsule, tablet, liquid or powder form, each of which have different concerns.

b) How operators handle supplements. What processing or preparation is being undertaken? Are there risks of which the supplement handler needs to be aware? What are they, not forgetting microbiological, chemical or foreign body hazards? This may include, for example:

   - ensuring that staff are aware, when handling supplements, of the need for high personal hygiene standards.
   - Supplement handlers should, where necessary, be aware of procedures to keep toxic substances, such as cleaning materials, separate from ingredients and products, or of procedures on a production line to check for and reduce the risk of foreign bodies such as glass or metal in products.

4.4 Personal hygiene

Personal cleanliness and clothing: The Codex General Principles (see Annex V) contain helpful general advice on these requirements.

Infected supplement handlers: The Codex General Principles contain helpful general advice on these requirements (see Annex V).

4.4.1 Basic requirements

These are as follows:

a) Personnel should keep as clean as is reasonable all parts of their person, clothing or overclothing liable to come into contact with the product; must keep any open cut or abrasion on any exposed part of their person covered, ideally with a company issued detectable blue metal strip plaster, which should be issued, signed out and checked at the end of production to ensure it is still in place. Normal plasters applied to wounds received outside of the workplace should ideally be removed and replaced with company issued plasters. If any plaster is lost during production this must be reported immediately to the relevant manager and the procedures for the control of foreign body contamination must be followed;

b) Personnel must not spit, smoke, use snuff or chew gum in any supplement production room or room in which there is open product. Food and drink must not be taken into or consumed in production areas;

c) Personnel should wear sufficient clean and washable or disposable overclothing (including headgear and, where appropriate, neck-covering and/or beard snood);

d) Persons suffering from, or carriers of, certain kinds of infection (typhoid, paratyphoid, any other salmonellae infections, or amoebic or bacillary dysentery or any staphylococcal infection, which could include an infected cut) likely to cause poisoning to the consumer, must not be allowed to handle the supplement or raw ingredients; personnel suffering from any such infection must inform the manufacturer who may be required to inform the relevant National Authority, depending on the legislation within the country of manufacture.

4.4.2 Best practice requirements

In addition to the basic requirements, Best Practice (adapted to national requirements) may involve:

a) the provision of safety footwear and suitable protective overclothing, and the laundering thereof;

b) the provision of a separate and suitably equipped changing room;

c) pre-employment medical checks or certification so that no person suffering from or a carrier of any of the specified kinds of infection is employed as a supplement handler. Visitors and contractors should be verbally requested, prior to entering a production area, to inform the relevant staff member of any recent illness that may pose a risk of contamination to products. Contractors should be asked to read the hygiene requirement specific to that part of the operation in which they are working;

d) the use of a personal medication procedure to control personal medicines such as decongestant nasal sprays and those for diabetes or asthma;

e) the active encouragement of personnel to report infections and skin lesions, and the encouragement of supervisory personnel to look out for signs and symptoms of such conditions;

f) the following of 'return to work' procedures after illness or holidays abroad with emphasis on diseases contracted during the period abroad;

g) the prohibition of the wearing of wrist watches and jewellery except for plain wedding rings or plain sleeper earrings (without studs) for pierced ears in 'open product' areas. There should be a clear policy on the type of jewellery permitted for medical, ethnic or religious reasons and the controls in place to reduce the risk of product contamination and ensure employees' health and safety;

h) where the risk exists, the carrying of loose items (including mobile phones) in the production areas should be restricted or prohibited. Outerwear (coats or overalls) should not have external pockets;

i) the removal of protective clothing before break periods and on leaving the production area;

j) the keeping of fingernails clean, short and unvarnished. False fingernails or nail varnish should not be worn due to the risk of foreign body contamination;

k) the use of procedures for hand washing, ensuring personnel wash hands before commencing work, on return to the production area, after toilet and rest breaks and after handling waste or cleaning. Antibacterial cream should be applied to hands after washing in areas of high microbiological sensitivity;

l) the use of a procedure to control glove issue to prevent them being a source of foreign body contamination. Personnel training should include the understanding that the wearing of gloves does not reduce the need for adequate hand washing;

m) the use of the correct procedures in the event of breakage of glass or hard plastic lenses in spectacles (see 3.4).

Section 5

Product and process development

5.1 General

A risk assessment should be conducted from the earliest stages of product and process development to eliminate or minimise potential hazards and to aid the incorporation of effective control parameters into the product design. A Hazard Analysis Critical Control Point (HACCP) study is one method that could be used to perform this risk assessment (see Annex II).

Basic checks should be made when developing a new product or making changes to an existing product to ensure that the final product complies with current legislation regarding safety and legality in the country of intended market and also that it meets consumer expectation within the intended circumstances of use. Testing and inspection procedures should be developed to enable the monitoring of relevant parameters and the application of corrective action should results fall outside specified limits.

Continued attention should to be paid to any changes in legislation to ensure that existing products maintain compliance in all areas of production (see 2.3).

The following sections provide a guide to the necessary checks that need to be made when developing a new product. These sections include requirements at the product development stage which do not necessarily fall directly under Good Manufacturing Practice (GMP). However, if the product development stage is not carried out correctly then even the best GMP may not produce a product that can be legally sold in the country of intended market. These checks are therefore extremely important to the quality of the final product.

The documentation that arises as part of the product development stage is an integral part of the GMP that follows as, for example, it can act as the standard for acceptance of raw materials, final product checks etc.

5.2 Check legality of ingredients for all intended markets

- compliance with any compositional legislation;
- all additives permitted and below maximum levels;
- official approval obtained for new/novel ingredients as necessary to comply with national rules that govern such ingredients;
- all components of compounded ingredients permitted;
- ingredients prohibited in the country of intended market not present;
- composition does not infringe patents;
- irradiated status.

5.3 Check safety of ingredients

- raw materials and final product meet microbiological criteria as applicable to ensure product safety and compliance with national rules;
- formula considered for potential chemical interactions;
- micronutrient levels (e.g. zinc, vitamin A) are within accepted safety levels and are appropriate for the target population;
- ingredients and final product comply with legislation on contaminants;
- where applicable, safety checks have been carried out on individual and combinations of herbs;
- potential allergen sources identified/substituted.

5.4 Check stability of formula

Products must meet the label claim throughout the period of declared shelf life and must meet the expectations of the consumer. Therefore, the person responsible for putting the supplement on the market has to determine the length of time during which the product, after being packed for sale, will comply with its label claims.

The determination of this date is based on the date of production and takes into account data from:

- stability studies on the actual product, either from real time testing or accelerated testing as determined most appropriate to the particular product by the manufacturer;
- use of previous data from other stability studies made on similar products, where appropriate;
- extrapolation of results from relevant bibliographic data.

In particular, it is recommended that the following factors are checked in normal conditions of storage:

a) organoleptic properties (taste, smell, presentation/appearance, colour) and notably:

- colour and flavour stability.

b) chemico-physical and microbiological properties, and notably:

- that the final product does not permit microbiological growth;
- fat stability (oxidation/rancidity in fish or vegetable oils);
- physical changes on storage (appearance, hardness);
- there are no interactions between ingredients (to confirm prior theoretical checks);
- claimed levels of ingredients are maintained throughout the shelf life;
- the stability in use of the product i.e. the stability of the product after opening the pack and during the expected consumption period.

These checks allow the manufacturer to ensure that the expiration (Best Before End) date is valid for declared ingredients.

5.5 Check legality of labelling

- mandatory information included is in compliance with relevant legislation
- genetically modified (GMO) ingredients:
  - a) includes all ingredients produced from genetic modification;
  - b) GMO source is approved for use in country of intended market;
  - c) labelling is in compliance with legislation:
- compositional statements (e.g. where applicable, laxative statement, indication of sweeteners) are in compliance with legislation and in the appropriate position;
- all potential allergenic sources are identified in the ingredients list in accordance with legislation;
- appropriate warnings are made for micronutrient levels (e.g. iron, vitamin A) where required nationally;
- all components of compounded ingredients are listed if required by legislation;
- the indication of the quantity of ingredients is in compliance with legislation;
- any products that have been legally irradiated or contain legally irradiated components, should be labelled appropriately in accordance with legislation;
- information is in the language(s) required by the intended market;
- all other legal requirements for product labelling are met for the country of intended market.

5.6 Check legality of claims

- check legality of intended claims under applicable law ensuring they do not contravene current legislation;
- where nutritional information is required by the intended market, energy (calorie) calculations are in compliance with legislation;
- vitamin and mineral calculations are in compliance with legislation;
- active components are correctly calculated, taking into account moisture, assay, levels etc.;
- dose of product in relation to intended claims is supported by scientific evidence;
- minimum levels for claims can be met at end of declared shelf life and can be met at lower end of raw material specification ranges;
- claims are not misleading and can be substantiated by generally accepted scientific evidence.

5.7 Check protection/appropriateness and legality of packaging (also see 6.5)

- packaging should be appropriate for the product with light/moisture/oxygen barriers;
- product contact surfaces of packaging should be in compliance with legislation;
- packaging recoverability (e.g. recycling) should be in compliance with legislation;
- check compliance with all relevant legislation for all packaging materials;
- select appropriate packaging that will maintain stability of the product throughout shelf life;
- packaging should not be misleading i.e. pack size should not be excessively larger than the contents volume;
- packaging should conform to minimum safety and hygienic standards for the packed product and consumer;
- statutory label information is legible, intelligible and in the appropriate position according to legislation.

5.8 Confirm by appropriate verification procedures that it can be made safely and consistently

- take into consideration tolerances on raw material specifications and the ability to meet claims at extremes of specification ranges;
- check homogeneity can be achieved by the mixing process;
- where appropriate, perform trials on production lot sizes to check de-mixing during in-process handling and packing;
- ensure raw materials and product are protected from effects of moisture/oxygen/light during storage and manufacturing processes;
- check tolerances on finished product specifications and the ability to meet claims at extremes of specification ranges;
- check integrity of pack seals/barriers to ensure packaging consistently seals.

Section 6

Manufacture

6.1 General

The operations and processes used in manufacture should, with the premises, equipment, materials, personnel and services provided, be capable of consistently yielding finished products which conform to their specifications and are suitably protected against contamination or deterioration. Defined and documented manufacturing procedures, including associated activities and precautions, are necessary to ensure that all concerned understand what has to be done, how it is to be done, who is responsible, and to avoid mistakes which could affect product safety and quality. Such procedures should be provided in the Master Manufacturing Instructions for each product. All personnel responsible for decision making or authorisation at any stage during the process should be formally defined.

6.2 Verification of production processes

Before the introduction of Master Manufacturing Instructions for a product, trials should be carried out to establish whether the formulation, methods and procedures specified therein are suitable for factory production, and are capable of consistently yielding products within the Finished Product Specification. If necessary, amendments and further trials should be made until these conditions are satisfied.

Similar evaluation should be carried out in connection with any significant proposed change of raw material, plant or method.

Similar evaluation should be carried out periodically, to check that the Master Manufacturing Instructions are being followed, that they still represent an effective and acceptable way of achieving the specified product and that they are still capable of consistently doing so.

Tests should be conducted in accordance with previously defined specifications and procedures and a record made of the results. The necessity, extent and degree of the work will depend on the nature and complexity of the product and process as determined by the manufacturer.

6.3 Documentation

Production staff should follow defined and authorised procedures for each stage of each manufacturing process, i.e. the manufacture of a product should proceed in accordance with the Master Formula and Method, and/or with the Master Manufacturing Instruction for each product and related Standard Operating Procedures. The details of the operation should be recorded on the Lot Manufacturing Record, or Lot Packaging Record.

Any deviation from defined procedures must only be by prior agreement, and must be recorded and agreed by the person responsible for quality control, or their assigned deputies.

Before any manufacturing operation begins, steps should be taken to ensure that the work area and equipment are clean and free from any starting material, packaging material, products, product-residues or documents not required for the current operation.

At all times during processing, all materials, bulk containers and major items of equipment used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and lot number. Where applicable, this identification should also indicate the stage of manufacture and status.

Operating instructions for production operators should be written in clear, unambiguous, instructional form and should form a key part of operator training. Due regard should be given to reading or language difficulties of some operators. Supervisors should confirm by observing and questioning the operator that the instructions, and significance of the instructions, are fully understood.

Particular attention should be paid to problems that may arise in the event of stoppages, breakdowns or other unexpected events that may alter the planned flow of production, and written instructions should be provided for action to be taken.

6.4 Raw materials/ingredients

Each raw material/ingredient should have and comply with its specification.

Each delivery lot should be given a reference code to identify it in storage and processing, and the documentation should be such that, if necessary, any lot of finished product can be correlated with the deliveries of the respective raw materials used in its manufacture and with the corresponding laboratory records. Deliveries should be stored and marked in such a way that their identities do not become lost.

Any pallets or deliveries should be cleaned if necessary before entering the warehouse.

Upon receipt, raw materials should be quarantined until inspected. Release can either be based on Certificates of Analyses provided by the supplier, or sampled and tested in accordance with agreed specifications, and released for use only on authority of Quality Control. Release should not be based upon supplier Certificates of Analyses until confirmation of the reliability of the supplier's test results has been obtained (see Annex V).

Particular care should be taken where a delivery of containers appears from markings to include more than one lot of the supplier's production, or where the delivery is of containers re-packed by a merchant or broker from a bulk supply. Where appropriate, immediate checks should be carried out for off-flavours, off-odours or taints, and testing should include test of identity, i.e. establishing that the substance is what it is purported to be. For multi-container deliveries, where it is impracticable to check the identity of the contents of every container on arrival, operators should be trained and encouraged to report immediately anything unusual about the contents when a fresh container is brought into use.

Operators should keep records of the suppliers of every lot of ingredient received, as part of the traceability system. Records must be kept available for inspection by the competent authorities for the period required by national legislation.

Temporarily quarantined material should be located and/or marked in such a way as to avoid risk of its being accidentally used. Material found to require pre-treatment before being acceptable for use should be suitably marked and remain quarantined until pre-treatment. Material found totally unfit for use should be suitably marked and physically segregated pending appropriate disposal.

In the case of a bulk delivery by tanker, preliminary quality assessment should be made before discharge into storage is permitted, and systems should be in place so that the material can be traced to a certified source.

All raw materials should be stored under hygienic conditions, and in specific conditions (e.g. of temperature, relative humidity) appropriate to their respective requirements as indicated in their specifications, and with due regard to any legislation relating to the control of hazardous substances.

Stocks of raw materials in store should be inspected regularly and sampled/tested where appropriate, to ensure that they remain in acceptable condition.

In issuing raw materials from store for production use, correct stock rotation should normally be observed, unless otherwise authorised or specified by Quality Control.

Authorised procedures and documentation should be established and followed for the issue of raw materials from store, (for example, Standard Operating Procedures).

When a raw material has been issued but not used as planned (e.g. because of a plant stoppage) Quality Control should advise as to its disposition.

Depending on the product being manufactured, the ingredients involved and the nature of the process and equipment, the dispensing of the required quantities of ingredients could take various forms, including manual dispensing by weight or volume, or continuous metering by volume; the form(s) actually taken should be stated within the Master Manufacturing Instructions. In each case, the weighing and/or measuring equipment should have the capacity, accuracy and precision appropriate to the purpose, and the accuracy must be regularly checked and documented (see also 3.5).

Where lot quantities of an ingredient have to be dispensed manually into containers in advance, this should be done in a segregated area. Where manual pre-dispensing of relatively small and accurate quantities (for example, of micronutrients or additives) is required, this should be done by, or under direct supervision of, suitably trained staff. All weighings should be checked by a second operator or by use of a validated computerised weighing control system.

Records should be kept to enable the quantities of materials issued to be checked against the quantity or number of lots of product manufactured.

Where an operator controls the addition of lot quantities of one or more ingredients to a lot, the addition of each ingredient to a lot should be recorded at the time on a Lot Manufacturing Record, to minimise risk of accidental omission or double addition.

The final yield, and any significant intermediate yield, of each production lot should be recorded and checked against the expected yield within defined limits. In the event of a significant variation, steps must be taken to prevent release or further processing of the lot (or of any other lots, or products processed concurrently, with which it may have become admixed) until an adequate explanation can be found which permits release or further processing.

6.5 Packaging and labelling materials

Each packaging material should have and comply with its specification (including any legal requirements), which should be such as to ensure that:

- the packaging is in compliance with the requirements of any relevant legislation on packaging and packaging waste;
- the packaging provides adequate protection to ensure the chemical and physical stability of the product during the declared shelf life under stated conditions of storage and use;
- in the instance of packaging coming into immediate contact with the product, there is no significant adverse interaction between product and packaging material, and that the packaging material complies with any relevant legislation governing product contact surfaces;
- where the packaged product undergoes subsequent treatment, whether by the manufacturer or consumer, the packaging adequately stands up to the processing conditions and no adverse packaging/product interaction occurs;
- the finished pack has ample space to carry the statutory and other specified information in the required form and location (see also 5.5).

Where packaging material carries information required by law (e.g. labels, printed packages, lithographed cans), Quality Control should ensure that the specification is updated as required to comply with new legal provisions, and that stocks of packaging materials that no longer comply are quarantined for modification (if possible and desired) or destruction.

When a new pack or label design is introduced for a product the obsolete packaging or labels should be destroyed and this disposal recorded.

Each label should contain a code or similar means of identification which will cross-reference it to the formulation to ensure that changes in formulation are reflected in the label copy.

Each delivery or lot of packaging should be given a reference code to identify it in storage and processing, and the documentation should be such that, if necessary, any lot of finished product can be correlated with the deliveries of the respective packaging materials used in its manufacture and with the corresponding quality inspection records. Deliveries should be stored and marked in such a way that their identities do not become lost.

Packaging materials should be assigned a shelf life where appropriate.

Deliveries of packaging material should be quarantined upon receipt and released for use only when the necessary quality assessment has been made. Operators should be trained and encouraged to report immediately anything unusual about the appearance, odour or behaviour of packaging materials issued.

Temporarily quarantined packaging material should be located and/or marked in such a way as to avoid risk of its being accidentally used before release. Material found totally unfit for use in packaging operations should be suitably marked and physically segregated pending appropriate disposal.

All packaging materials should be stored in hygienic conditions, and as indicated in their respective specifications.

Stocks of packaging materials in store should be inspected regularly to ensure that they remain in acceptable condition.

In issuing packaging material from store for production use, stock rotation should normally be observed, unless otherwise authorised or specified by Quality Control.

Authorised procedures and documentation should be established and followed for the issue of packaging materials from store, and for the return of part-used lots of packaging to store. The returns procedure should consider the need to re-seal part used boxes of packaging to prevent foreign body contamination.

All printed packaging components should be issued from and returned to a secure area with controlled personnel access

There should be a procedure for the reconciliation of all printed packaging component stock from quantity issued, quantity used, wastage and that returned to store.

6.6 Processing and packaging

Where a company manufactures more than one product or more than one version of a product, and there is more than one production line, production layout should be such that confusion is avoided.

Whether in single-line or multiple-line production particular care should be taken, in terms of production layout and practices, to avoid cross-contamination of one product by another.

Multiple packaging lines should have adequate segregation in order to avoid cross-contamination.

On a production line, the name and appropriate reference to the product being processed/ packaged should be clearly displayed.

Where a company manufactures more than one product, or more than one version of a single product, the greatest care should be taken to check that the correct packaging is issued for the product to be manufactured, and that no incorrect packaging materials, left over from a previous production run of a different product or a different version, are left in the production area where they might accidentally be used. In no circumstances should primary product packaging be used for other than its intended purpose.

Where packaging is reference-coded and date-marked for use, care should be taken to ensure that only material carrying the correct reference and date codes are used. Surplus material left from earlier production and bearing an invalid reference or date should not be left in the production area. Where the reference and/or date is applied during the manufacturing operation, care should be taken to check and ensure that the marking machine is set for the correct reference and date.

Before production begins, checks should be carried out to ensure that the production area is clean and free from any products, product residues, waste material, raw materials, packaging materials or documents not relevant to the production to be undertaken; and that the correct materials and documents have been issued and the correct machine settings have been made. All plant and equipment should be checked as clean and ready for use.

Processing should be strictly in accordance with the Master Manufacturing Instructions subject to any variations approved, and by detailed procedures set out for operators in the Plant Operating Instructions.

Process conditions should be monitored and process control carried out by suitable means including, as appropriate, sensory, instrumental and laboratory testing, and on-line checking of correct packaging and date-marking. Where continuous recorders or recorder/controllers are in use, the charts should subsequently be checked by Quality Control and retained as process records.

There should be regular and recorded checks on the accuracy of all instruments used for monitoring processes (e.g. thermometers, temperature gauges, pressure gauges, flowmeters, checkweighers).

Effective cleaning of production premises and equipment must be carried out.

All persons working in or visiting the production area must comply with the requirements of personal hygiene, and adequate facilities must be provided, and appropriate clothing worn (see also 3.4.6 and 4.4).

General 'good housekeeping' should be practised, including prompt removal of waste material, precautions to minimise spillage or breakage, prompt removal and clean-up of any spillage or broken packaging occurring, and the removal of any articles that might enter the product as foreign matter.

6.7 Intermediate products

After its preparation, an intermediate product should be quarantined until checked and approved by Quality Control for compliance with its specification. If required to be stored before further processing, it should be stored as designated in that specification, and suitably reference-marked and documented so that it can be correlated with the lots of raw materials from which it was made and the lot(s) of finished product in which it is subsequently incorporated.

A lot of intermediate product found to be defective should remain quarantined pending re-working or recovery of material or outright rejection as the case may be (see Section 7).

6.8 Finished products

Packed finished products should be quarantined until checked and approved by Quality Control for compliance with the appropriate Finished Product Specification and not released for sale until reconciled, approved and signed-off by the appropriate person.

An approved lot of finished product should be suitably flagged to identify it, and stored under the appropriate conditions (e.g. of temperature or relative humidity) stated in the Finished Product Specification. Each lot of finished product should bear an identification mark that will provide a means of tracing product to any retailer to whom part of that lot is sold.

Where a lot of finished product fails to meet the Specification, the reasons for failure should be thoroughly investigated.

Defective finished product should remain quarantined pending re-working or recovery of materials or disposal as the case may be.

6.9 Disposal of waste and effluent

It is essential when disposing of surplus raw materials, waste or reject product, process chemicals and laboratory reagents that attention is paid to all legislative requirements for waste.

Disposal of printed packaging materials or raw materials and rejected products should be carefully controlled and a reconciliation should be carried out on quantities used and/or produced against those being destroyed.

Waste management protocols should take the following into consideration:

- waste minimisation;
- reusing the material wherever practical;
- waste recycling;
- waste disposal.

All waste materials and effluent should be disposed of in accordance with current local regulations by a route appropriate to the class of material. All disposal must be appropriately documented.

Section 7

Recovery or re-working of materials

Material may be recovered, re-worked or re-processed by an appropriate and authorised method, provided that the material is suitable for such treatment, that the resulting product complies with the relevant specification and that the related documentation accurately records what has occurred.

Recovered material must be identified and quarantined until the material review is conducted and a disposition decision is made.

All procedures of acceptance, tests, treatments, sampling, authorising or rejection of recovered materials should be carried out according to the Standard Operating Procedures.

Residues and re-worked or recovered material which might adversely affect product quality, efficacy or safety should not be used in subsequent lots.

The treatment of product residues and re-worked or recovered material, and the means of their inclusion in a subsequent lot, should be specifically authorised and documented.

Limits, approved by Quality Control, should be established for the amount of any such material which may be added to a subsequent lot.

Lots incorporating residues should not be released until the lots from which the residues originated have been tested and found suitable for use.

Methods of re-processing should be specifically authorised and fully validated and documented once any potential risks have been evaluated and found negligible.

The need for additional testing of any Finished Product which has been reprocessed (or to which residues have been added) should be considered.

A finished product returned from the manufacturer's own stores or warehouse (because, for example, of soiled or damaged labels or outer packaging) may be relabelled, or bulked for inclusion in subsequent lots, provided that there is no risk to product quality and the operation is specifically authorised and documented. If such products are re-labelled, extra care is necessary to avoid mix-up or mislabelling; care should be taken to ensure that any re-labelled product is appropriately date-marked and reference-coded to permit product traceability.

Finished products returned from the market and which have left the control of the manufacturer should be considered for re-sale, re-labelling or bulking with a subsequent lot only after they have been critically assessed by Quality Control. 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 re-processing to recover active ingredients may be possible.

All records relating to recovery, re-working or re-processing must be kept for a previously decided period, with consideration given to any legal requirements.

Section 8

Storage

8.1 General

Effective storage operations should be designed to ensure that all products are easily accessible for load assembly as required; to ensure that aisles and assembly areas are planned so that unimpeded movement is possible to and from all parts of the storage area; to facilitate proper stock rotation such as first in first out, particularly important in relation to short-life and date-marked products; and to obtain maximum utilisation of available space, consistent with the foregoing requirements.

Storage and transportation of finished products should be under conditions that will prevent contamination, including development of pathogenic or toxigenic micro-organisms, will protect against undesirable deterioration of the product and the container, and assure the delivery of safe, clean and wholesome products to consumers. This deterioration includes, but is not limited to, contamination from insects, rodents and other vermin, toxic chemicals, pesticides and sources of flavour and odour taint.

The buildings, grounds, fixtures and equipment of product storage areas and vehicles should be designed, constructed, adapted and maintained to facilitate the operations carried out in them and to prevent damage.

8.2 Access to storage areas

Access to material and product storage areas should be restricted to those working in those areas and to other authorised persons.

A suitable curtain should be provided at all entrances and exits in order to maintain the internal conditions of the storage area at an appropriate level for the product therein.

When the storage area is connected directly to the manufacturing area, a buffer area/pass box should be provided between the storage area and the manufacturing area.

8.3 Temperature and lighting

Storage area temperatures should be kept at an appropriate level to maintain the wholesomeness of the particular products received and held in such areas. Temperature mapping and recording should be carried out initially to ensure uniform temperatures in product storage areas, and repeated as frequently as is considered necessary.

The lighting should be as high as possible above the product, as the lower the lights are positioned on the wall, the greater the shadows created by the pallets/shelves.

Lights should be protected by shatterproof covers where appropriate.

8.4 Product storage

In order to provide effective protection from contamination, materials and products should be stored under conditions stated in their respective specifications. Particular attention should be paid to the avoidance of microbiological cross-contamination and tainting. Where special conditions are required, they should be regularly checked for compliance.

Materials and products should be stored in such a way that cleaning, the use of pest control materials without risk of contamination, inspection and sampling, retention of delivery identity or lot identity, and effective stock rotation can be easily carried out.

The stacking of product should have regard for all elements of safety. Pallets should be visually checked periodically for structural integrity. Where appropriate, cornerboards should be positioned at the corner of each stack, both to make the corner 'stand out' visually, and to protect the product from accidental impact damage by high lift and powered pallet trucks.

Pallets should be placed in prescribed places; gangways should be kept clear and not used for temporary storage of materials. Pallets should be so spaced as to allow proper ventilation.

Products which have been recalled or returned, and lots which have been rejected for re-working or recovery of materials or disposal, should be so marked and physically segregated, preferably in an entirely separate storage facility.

Material deliveries and product lots temporarily quarantined pending the results of testing, should be so marked, suitably segregated, and effective organisational measures implemented to safeguard against unauthorised or accidental use of those materials or despatch of those products. A suitably consistent control system should be used.

All stored items should be marked with their identification to ensure that traceability is maintained.

If a lot of finished product is temporarily stored unlabelled, to be labelled at a later date, the greatest possible care should be exercised in maintaining its exact identity. The containers holding the product must bear a fixed label of contents and lot/batch/identification number and the final product label must be marked with the appropriate shelf life. This information may be available from the documentation or identified from the product name and lot/batch number.

8.5 Damaged goods

Damaged goods should be placed in a designated place as they are discovered. Care must be taken not to expose stored product to contamination or infestation. The same may also apply to returns from customers. Damaged goods which cannot be re-packed must be dealt with prior to disposal so as to prevent their accidental re-entry into the distribution chain.

Only products which have been properly inspected to ensure that the product and packaging are fully acceptable may be re-packed into outer packaging in a suitable area/room. If it is necessary to re-pack goods of different production codes into the same outer-packaging, the package should be marked with an age code which relates to the oldest packet in the case.

8.6 Cleaning of storage areas

Effective cleaning of storage premises and equipment must be carried out at the frequency and using the methods and materials specified in well designed cleaning schedules and instructions. Cleaning materials should be stored in a separate location to the raw materials/ product in order to avoid contamination or tainting (see also 3.4.4).

Storage areas should be regularly inspected for cleanliness and good housekeeping, and to identify lots of products which have exceeded their shelf-life or, in the case of date-marked products, leave insufficient time for retail display. These inspections should be formally documented, including any corrective action taken if necessary.

Section 9

Transport and distribution

All vehicles, containers etc. should be free from rodents, birds and insects or contamination from them; free from odours, nails, splinters, oil and grease, accumulations of dirt and debris, and should be in good repair, without holes, cracks or crevices that could provide entrances or harbourage for pests. Contaminated vehicles, containers etc. should be kept in a separate area away from those that are clean.

Prior to loading, it is advisable that the vehicle interior (including walls, floor and ceiling) be inspected for general cleanliness, freedom from moisture, foreign materials, etc. which could cause product contamination or damage to the packages.

Vehicles bringing product to a storage area should be inspected for evidence of damage (including that to any lighting or other "brittle material", for example, glass, ceramic or hard plastic items), or of insect or rodent infestations, objectionable odours or other forms of contamination.

If damaged product is accepted on a vehicle it must be kept separate from other product and handled in a manner which will not expose other products on the vehicle, or subsequently the storage area, to contamination or infestation.

A procedure should be set up to deal with consequences of accidents and damage occurring when goods are in storage or distribution, e.g. salvage or condemnation following damage to goods in a road traffic accident.

Security precautions should include means of deterring and preventing any tampering with goods in storage and distribution.

Where warehousing (storage) or transport is contracted out, the premises, vehicles and conditions, where possible in practice, should be subject to checks to ensure that there is no risk of contamination or tainting.

To reduce the occurrence of physical changes in the product (for example, melting of soft gel capsules), instructions should be given when particular care is needed to reduce large temperature fluctuations during transport and delivery.

Docks, railway sidings, bays, driveways, etc., when within the factory complex, should be kept free from accumulation of debris and spillage.

Fire appliances should be suitable for use on the commodities concerned and a sufficient proportion of them should be capable of dealing with electrical and petroleum/fuel oil fires.

Fork lift and other trucks used within the storage areas should normally be battery driven or otherwise equipped to prevent fume or fuel contamination.

Section 10

Documentation

10.1 General

Good and effective documentation is an essential and integral part of GMP. Its purposes are to define the materials, operations, activities, control measures and products; to record and communicate information needed before, during or after manufacture; to reduce the risk of error arising from oral communication; and to permit investigation and tracing of defective products. The system of documentation should be such that, as far as is practicable, the history of each lot of product, including utilisation and disposal of raw materials, intermediates and bulk or finished products, may be ascertained and thus traceability maintained.

Where documentation is maintained electronically safeguards need to be in place to ensure the data is entered correctly and that sufficient back-ups are made so that, in the event of file alteration, corruption, deletion or destruction, the original data can be retrieved. The system should be protected against unauthorised access to the data. Procedures should be developed outlining the issue, cancellation or alteration of authorisation, and also for the action to be taken in the event of system failure or breakdown.

Any computer software used for controlling critical operations such as quarantine/ release status should be set-up to only permit approved-personnel access and 'change control'.

To facilitate proper and effective use of documents they should be designed and prepared with care, be free of errors and pay particular attention to the following points:

a) The title (which should be unambiguous), nature and purpose of the document should be clearly stated. The document should be laid out in an orderly fashion, and be easy to check. Where a document has been revised, systems should be operated to prevent inadvertent use of superseded documents;

b) It is an advantage if it is possible to revise part of a document without necessarily completely rewriting the whole;

c) The way the document is to be used, and by whom, should be clearly apparent from the document itself. Other means provided to explain its use are of less value;

d) Where documents bear instructions they should be written in the imperative, as numbered steps. They should be clear, precise, unambiguous and in language the user can understand. Such documents should be readily available to all concerned with carrying out the instructions;

e) Documents which require the entry of data should:

   – provide sufficient space for the entry, including space to record preventive and corrective actions taken following inspection as applicable;

   – allow adequate spacing between the entries;

   – show headings clearly indicating what is to be entered;

f) Persons making entries should do so in clear legible writing and should confirm the entry by adding their initials or signatures, which have been previously authorised by the manufacturer. A signed recorded observation is preferable to simply ticking in a box;

g) Manuscript entries should be made in ink or other indelible medium;

h) The size and shape of documents and the quality and colour of the paper used should be considered in relation to the typing/printing, reproduction and filing facilities available; Reproduced documents should be clear and legible.

Sufficient training on how to complete the documents should be given to the relevant personnel and the effectiveness of the training should be regularly assessed. It should be ensured that personnel using and/or completing the documents are literate in the language used in the documentation (see also 4.2).

Documents should contain all necessary, but no superfluous, data. Any headings, or places for entries, which cease to be used should be removed at the earliest opportunity.

If an error is made or detected on a document it should be corrected in such a manner that the original entry is not lost and the correction initialled and dated. Where appropriate, the reason for the correction should be recorded. The use of correction fluid, tape or pens is not allowed.

Documents should be kept up to date. Any amendments should be formally authorised and signed by the previously authorised responsible person. In the case of amendments, the amended document should be replaced at the earliest opportunity by a newly prepared document.

The documentation system should include procedures for issue, authorisation, distribution, periodic review and revision.

An outdated or superseded document should be removed from active use, and a copy, marked that it has been superseded, retained for reference. Routine internal audits will help ensure that the correct versions of documents are being used.

It may be useful to prepare a manual which describes the overall Quality Assurance system, the procedures employed and the documents used. This should be available to all relevant staff.

10.2 Types of documents

Manufacturing formulae and processing and packaging instructions state all the starting materials used and lay down all processing and packaging operations.

Specifications describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Procedures give directions for performing certain operations, e.g. cleaning, clothing, environmental control, sampling, testing, equipment operation.

Records provide a history of each lot of product, including its distribution, and also of all other relevant circumstances pertinent to the quality of the final product.

10.3 Retention of documents

The retention period for documents is dependent upon their function. Consideration must be given to any legal requirements, including the provision of evidence of due diligence. As a general guide:

a) Lot records should be retained for the shelf life of the product plus an additional year;

b) Weights and measures control records should be retained for a minimum of one year and one day.

Retention of personnel data should be in accordance with national data protection laws.

A Controlled Records List should be used to provide an ongoing and constantly monitored system for removing the files of unwanted old data.

Fire-risk should be assessed and consideration should be given to the use of a fire proof safe for the storage of electronic backups and, in the case of paper-only systems, master copies and key documents.

10.4 Classes of documents

The following lists are not exhaustive but do give an indication of the types of documents which are advisable:

a) Specifications, Instructions and Procedures:

- Ingredient specifications;
- Packaging materials specifications;
- Copy of order and/or terms of conditions of purchase;
- Master manufacturing instructions (including standard recipes);
- Intermediate specifications;
- Bulk product specification;
- Finished product specifications;
- Quality control (including analytical and microbiological) procedures and methods;
- Standard procedure for product recall;
- Plant operating instructions;
- Cleaning instructions, good housekeeping and pest control schedules;
- Plant maintenance schedules;
- Quality Assurance programme.

b) Records and reports

- Records of receipt, test reports, approval and issue for use of raw materials and packaging materials;
- Records of the testing and release of intermediates, bulk products and finished products;
- Records of process control tests;
- In-process recording instruments charts;
- Weight or volume control charts;
- Lot manufacturing records;
- Records of authorisation of distribution of the product;
- Contracts held for the subcontracting of production, distribution, analysis etc;
- Customer complaint records;
- Quality control summaries and surveys;
- Quality audit reports and records;
- HACCP review reports (as applicable);
- Training records;
- Superseded documents.

c) Programmes

- Production programmes;
- Calibration programmes;
- Validation/verification programmes;
- Training programmes;
- Quality audits.

Section 11

Complaints procedure, product recall and emergency procedure

11.1 General

If a supplement business operator/company considers, or has reason to believe, that a supplement which it has imported, produced, manufactured or distributed is not in compliance with applicable safety requirements, it shall immediately initiate procedures to recall the supplement in question from the market. The operator should also inform the appropriate authorities where the product(s) is marketed of the problem and collaborate with the authorities on action taken to avoid or reduce risks posed by the supplement.

If the product has already reached the consumer, the operator should also consider whether it is appropriate to extend the recall to consumers, possibly by a public announcement.

11.2 Complaints

Quality complaints should be evaluated by individuals who have an understanding of the full significance of a complaint and who may also have knowledge of other related complaints. A procedure must therefore be provided for appropriate channelling of all quality complaint reports.

The system for dealing with complaints should follow written instructions which indicate the responsible person through whom the complaints must be channelled.

If the responsible person is not the Quality Control Manager, the latter should be fully informed and closely consulted. The responsible person should have the appropriate knowledge and experience, and the necessary authority, to decide the action to be taken.

Where possible, product quality complaints should be thoroughly investigated by appropriately qualified personnel and a report prepared as a basis for action and for the records.

Action should include responding to the complainant, and must include responding to any enforcement authority involved. Where the complaint is justified, steps to remove or overcome the cause and thus prevent recurrence should be taken; and the defective material which the complaint sample might represent should be dealt with, including possibly a product withdrawal or recall.

Complaints reports should be regularly analysed, summarised and reviewed for any trends or indication of a need for a product recall or of any specific problem requiring attention. It is strongly recommended that appropriate summaries include comparative data and that they are regularly distributed to directors and senior management.

11.3 Product withdrawal and recall

The withdrawal of a product is the action taken to have the product returned to the manufacturer from the customer/retailer but not from the final consumers. Withdrawal of a product may be a voluntary action by the company, following concerns of product quality but not necessarily product safety. The recall of a product is the action taken to have a product returned to the manufacturer from the customer/retailer and from the final consumers. Product recalls are often made in response to safety concerns.

A product defect coming to the manufacturer's attention, whether through a complaint or otherwise, may lead to the need for a product withdrawal or recall. There should be a pre-determined written plan, clearly understood by all concerned, for the withdrawal or recall of a product or a known lot or lots of product known or suspected to be a safety risk or otherwise unfit, or of wholesome but sub-standard product which the manufacturer wishes to withdraw or recall. A crisis procedure and management team should be established.

A responsible person, with appropriate named deputies, should be nominated to initiate and co-ordinate all withdrawal and recall activities, and to be the point of any contact with regulatory authorities on recall matters.

Out of hours contact details of key personnel and regulatory authorities should be kept in an accessible form and regularly updated.

The design of manufacturing records systems and distribution records systems, and the marking of outer cartons and of individual packs, should be such as to facilitate effective withdrawal or recall if necessary. A good system of lot marking will pinpoint the suspect material and help avoid excessive recall.

There should be written withdrawal and recall procedures, and these should be capable of being put into operation at short notice, at any time, inside or outside working hours.

The withdrawal and recall procedures should be shown to be practicable and operable within a reasonable time by carrying out suitable testing of the procedure.

The withdrawal and recall procedures should be reviewed regularly to check whether there is need for revision in the light of changes in circumstances or of the responsible person.

Product withdrawals or recalls may arise in a variety of circumstances which, usually, fall into three main categories:

a) where the national or local authorities become aware of a safety risk or suspected safety risk, and information and co-operation from the manufacturer or importer is necessitated;

b) where the manufacturer, importer, distributor or retailer becomes aware of a safety risk or suspected safety risk;

c) where there is no safety risk or suspected safety risk involved, but there is some circumstance (e.g. sub-standard quality, mislabelling) which has come to light and which prompts the manufacturer, importer or retailer to decide to withdraw or recall the affected product.

In case (c), the company will itself have to organise the withdrawal or recall operation. In cases (a) and (b), consideration may be given to issuing a public warning. Generally this would be done in consultation with the manufacturer or importer, the distributor or retailer, and any relevant enforcement authority interest. Normally any arrangements for withdrawal would be discussed so that the most appropriate methods could be effected or endorsed by the authorities, and would also take into account any requirements for or arising from the information indicated below.

Although a defect or a suspected defect leading to withdrawal or recall may have come to light in respect of a particular lot or lots or a particular period of production, urgent consideration should be given to whether other lots may also have been affected (e.g. through use of a faulty material or a plant or processing fault), and whether these should also be included in the recall.

The withdrawal or recall system should lay down precise methods for notifying and implementing a recall from all distributive channels and retailers where the affected product might be, as well as affected goods in transit, and of halting any further distribution of affected goods. Procedures should also be laid down for recalling product from consumers as necessary.

Notification of withdrawal or recall should include the following information:

- name, pack size and adequate description of the product;
- identifying marks of the lot(s) concerned;
- the nature of the defect;
- action required, with an indication of the degree of urgency involved;
- name of contact and telephone number of contact who can supply further information.

Withdrawn or recalled material should be quarantined, pending a decision as to appropriate treatment or disposal. Quantities of the withdrawn or recalled lot of product, at their identified locations, should be reconciled with the total lot quantity in question.

11.4 Emergency procedure

Regrettably, the possibility of real or threatened safety risk arising from the actions of second or third parties must be faced (e.g. deliberate contamination or poisoning of product or ingredient by extremists or otherwise misguided persons). Although some of the additional action that might be taken in such circumstances could be considered outside the scope of this Guide, it is included because those concerned in the manufacturing operation would very probably become involved.

The first intimation of a problem in this area could come from a whole variety of sources, e.g. consumer complaint, from a retailer, the media, the police, the enforcement authorities, employees, or by telephone, post or personal contact with any company location or any employee at any time.

It is therefore essential that any personnel engaged in manufacture should be aware of company action to be followed in dealing with such threats both within and outside of normal working hours, and that suitable arrangements exist for calling in key personnel out of hours in such an emergency. The extent to which any such emergency procedures may override normal lines of management should be explicitly stated, and these procedures should be formally documented.

Faced with an emergency situation, the withdrawal and recall procedures described above will apply, while the expertise of those involved in Quality Control and other relevant functions should be put at the disposal of the crisis management team responsible for handling the emergency.

The possibility of such sabotage and even site invasion may indicate a need for particular security precautions in vulnerable areas, e.g. locked rooms, use of seals, etc.

Cases of intentional or malicious contamination should be reported to the police for their involvement.

Any emergency or recall situation is likely to involve retailers or wholesalers, and a smooth and effective interface with their procedures should be achieved as early as possible during the crisis.

Section 12

Self inspections

Principle

Self inspections should be conducted in order to monitor the implementation and compliance with GMP principles and to propose necessary corrective measures. These should cover:

- personnel matters;
- premises;
- equipment;
- documentation (including the HACCP system as applicable);
- production;
- quality control;
- distribution of the products;
- arrangements for dealing with complaints and recalls.

Self inspections should be conducted at intervals, at least once a year, following a prearranged programme in order to verify their conformity with the principles of Quality Assurance.

Self inspections 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.

The person(s) conducting the self-inspection should call the attention of the relevant manager(s) of the company to the result of the inspection and any necessary corrections. The agreed corrections should be completed within a specified period of time. All self inspections should be recorded and reviewed periodically by senior management. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures and corresponding time frames for completion. Statements on the actions subsequently taken should also be recorded. The self-inspection records and reports should be retained for a pre-determined period of time.

Section 13

Sub-contracting operations

13.1 General

Where complete or part manufacture is carried out as an own-label, private label, distributor's own-brand, contract packing or similar operation, the obligation is on the Contract Acceptor/ Consignee (manufacturer) to ensure that production is carried out in accordance with GMP in the same way that would be expected were he manufacturing for distribution and sale on his own account, except where responsibility is specifically excluded by mutual agreement between the Contract Giver/Consignor (customer) and the Contract Acceptor.

The Contract Acceptor should ensure that the terms of the contract are clearly stated in writing (including a Technical Agreement between the two parties – see 13.2 below). It is essential to ensure that raw materials, intermediates and end products are covered by adequately full specifications (as outlined in other chapters). Any special GMP requirements should be clearly emphasised, and quality control, record transfer, coding, rejection, dispute and complaint procedures be identified and agreed.

It is normal practice for Contract Givers to impose contractual conditions that ensure quality standards and best practice. This is frequently achieved in the first instance by a visit to the manufacturing unit, whether at home or abroad, by the Contract Giver's auditors. The visit should include the following objectives:

a) to ensure that within the manufacturing environment the supplement can be produced safely;

b) to agree on a detailed product specification covering all aspects of product, process, pack and delivery, embracing parameters to be used for acceptance or rejection, and any legal requirements relating thereto;

c) to agree on levels of sampling of finished products by the Contract Giver and sample plans to be used in case of dispute;

d) to evaluate the adequacy of the control resources, systems, methods and records of the manufacturer;

e) to agree, wherever possible, objective methods of examination, while subjective measurements should conform to recognised and accepted standards if possible;

f) to agree the period for record keeping.

Agreement in all six areas is generally essential for any manufacturer/Contract Giver trading relationship and should benefit both parties.

When the Contract Giver requests amendments or improvements by the Contract Acceptor, these changes should be well documented and confirmation of acceptance of the completed work should be recorded.

13.2 Technical agreement

A technical agreement is a useful method of clearly defining the responsibilities of each party with regard to the above.

Particular attention should be given to clarify the responsibilities of each party in relation to key/critical activities, such as:

- the scope of the instructions given by the Contract Giver to the Contract Acceptor;
- approval and release of raw materials;
- changes to the formulation and processes;
- release specification;
- release of the finished product and its transportation;
- complaints and recall procedure;
- the procedure for notifying the Contract Giver of any abnormalities during the contracted process.

Any agreement may also include a section on the ownership of intellectual material (e.g. formulae, specific processing techniques), together with any restrictions on the transfer of information to third parties. Items of possible confidentiality should be identified and any appropriate safeguards be mutually agreed.

Section 14

Laboratory testing

A Quality Control laboratory should have appropriate premises, facilities, equipment and staff, and be so organised to enable it to fulfil GMP and Good Laboratory Practice (GLP) requirements and complement the scale of the manufacturing operations.

Both staffing and facilities will depend on the nature of the product range and the amount of testing required. It is essential that the facilities are appropriate to the needs of the tests.

Testing can be augmented by approved external laboratories who are accredited for the specific analysis required. Accreditation should be recognised by official national or international authorities. The scope of the accredited analysis should cover the sample matrix, that is, the relative combination of the components of the sample. If not, sample specific validation should be applied.

Staff should be appropriately trained and high standards of work should be set and maintained by rigid adherence to approved and agreed methods and method checks.

Quality Control laboratories should be designed and equipped to suit the operations required. Space should be made available for writing and the storage of documents and records and for any special provisions such as the storage of samples etc. at the appropriate temperature.

All laboratory equipment and instrumentation should be appropriate to the approved test procedures, and should be regularly serviced and calibrated by assigned persons or organisations.

Records of each service and calibration must be maintained for each piece of equipment. These records should also identify when the next service or calibration is due.

Written operating procedures should be available for each instrument or piece of equipment, and all personnel operating the equipment should be trained and familiar with the operating procedures.

Where necessary, analytical methods should include a control step to verify that the instrument or piece of equipment is functioning accurately. Defective instruments or equipment should be withdrawn from the possibility of use until the fault has been rectified.

All equipment should be maintained to a high standard of cleanliness in accordance with written procedures.

All personnel should wear clean protective clothing appropriate to the tasks being carried out, especially eye protection.

The disposal of laboratory waste material should be carefully and responsibly undertaken.

Samples should be analysed according to written procedures, using internationally accepted test methods or other methods that have been scientifically validated for the required sample matrix. Validation should generally consist of the following parameters: specificity / selectivity, recovery, precision, linearity and range, accuracy and Limit of Detection (LOD)/Limit of Quantitation (LOQ). Details of the validation should be available and retained.

Reagents made up in the laboratory should be prepared following defined procedures, dated upon receipt or preparation, and labelled with their concentration, standardisation factor, shelf-life and storage conditions as applicable.

Reference standards and secondary standards prepared from them should be dated and carefully stored, handled and used to maintain their quality. Furthermore, reference standards and their secondary standards should be labelled with their concentration, standardisation factor, shelf-life and storage conditions as applicable.

Written procedures should be developed for sampling and should specify the method and rate of sampling, equipment and type of sample container to be used, amount of sample required, any special precautions to be taken, instructions for any subdivision of the sample, storage and handling requirements prior to testing and the cleaning and storage of sampling equipment.

Samples should be labelled with the contents, sample identification number and date taken.

Results should be within the validated range of the method used.

Spreadsheets used for calculation of the sample concentration should be validated.

Detailed records should be maintained of all tests and analyses performed in the laboratory. Records should be dated and initialled by the responsible analyst and a second responsible person from Quality Control (or Quality Assurance). Records of sampling data, analysis data and calculations for the sample, should be properly identified in order to facilitate traceability.

The length of time for the storage of documents, records and samples should be consistent with the requirements for the manufacturing records.

For further information on GLP see Annex V.

Annex I

General glossary of terms

Analytical Method
A detailed description of the procedures to be followed in performing tests for assessing conformity with the **specification**.

Analyte
The component of a sample that is being analysed.

Audit
Systematic, independent and documented process for obtaining **audit evidence** and evaluating it objectively to determine the extent to which **audit criteria** are fulfilled.

Audit Criteria
Set of policies, **procedures** or **requirements**.

Audit Evidence
Records, statements of fact or other information which are relevant to the **audit criteria** and are verifiable.

Auditor
Person with the demonstrated personal attributes and **competence** to conduct an **audit**.

Batch
See **Lot**.

Buffer Area
An enclosed space between the **storage area** and the manufacturing area, often with positive pressure system, with the aim of reducing the contamination of processes and materials.

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

Characteristic
Distinguishing feature.

Competence
Demonstrated ability to apply knowledge and skills.

Conformity
Fulfilment of a **requirement**.

Contract
Binding agreement.

Contract Manufacture
Manufacture or partial **manufacture** ordered by one person or organisation (the contract giver) and carried out by a separate person or organisation (the contract acceptor).

Corrective Action
Action to eliminate the cause of a detected **nonconformity** or other undesirable situation.

Customer
Organisation or person that receives a **product**.

Defect
Non-fulfilment of a **requirement** related to an intended or specified use.

Documentation
All written **procedures**, instructions and **records, quality control** procedures and recorded test results involved in the **manufacture** of a supplement.

Effectiveness
Extent to which planned activities are realised and planned results achieved.

Finished Product
A supplement which has undergone all the stages of **manufacture**.

Information
Meaningful data.

Ingredient
Any substance that is used in the **manufacture** of a supplement and that is intended to be present in the **finished product.**

Inspection
Conformity evaluation by observation and judgment accompanied as appropriate by measurement, testing or gauging.

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

Legislation
The law, or group of laws, which are enacted by the authoritative body in a country or state of intended market.

Lot
A quantity of any 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 **lot** is its homogeneity).

Lot Manufacturing Record
A document stating the materials used and operations carried out during the **manufacture** of a given **lot**, including details of in-process controls and the results of any **corrective action** taken. It should be based on the **Master Manufacturing Instructions** and be compiled as the manufacturing operation proceeds.

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

Management
Coordinated activities to direct and control an **organisation**.

Management System
System to establish policy and objectives and to achieve those objectives.

Manufacture
The complete cycle of production and **quality control** of a supplement from the acquisition of all materials through all stages of subsequent processing, **packaging** and storage to the distribution or release of the **finished product.**

Manufacturer
The person or business that is involved in the manufacture of a finished product.

Master Manufacturing Instructions
A **document** or documents identifying the **raw materials**, with their quantities, to be used in the **manufacture** of a supplement, together with a description of the manufacturing operations and **procedures** including identification of the equipment and facilities to be used, processing conditions, in-process controls, **packaging materials** to be used and instructions for the removal of **finished product** to storage.

Measuring Equipment
Measuring instrument, software, measurement standard, reference material or auxiliary apparatus or combination thereof necessary to realise a **measurement process.**

Measurement process
Set of operations to determine the value of a quantity.

Nonconformity
Non-fulfilment of a **requirement**.

Objective Evidence
Data supporting the existence or authenticity of something.

Operator
The owner or person responsible for a manufacturing business.

Organisation
Group of people and facilities with an arrangement of responsibilities, authorities and relationships.

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 supplement, such as containers, closures, bags, packing, label materials (labels, inserts, etc.), seals, binding materials, adhesives and tapes.

Pass Box
Box providing a **buffer area** for material pass through.

Preventive action
Action to eliminate the cause of a potential **nonconformity** or other undesirable potential situation.

Process
Set of interrelated or interacting activities which transform one or more of the properties (physical, chemical, microbiological, sensory) of the **raw materials.**

Procedure
Specified way to carry out an activity or a **process**.

Product
Result of a **process**.

Quality
Degree to which a set of inherent **characteristics** fulfils **requirements**.

Quality Assurance
Part of **quality management** focussed on providing confidence that **quality** requirements will be fulfilled. Mainly focussed on intended product.

Quality Control
Part of **quality management** focussed on fulfilling **quality** requirements. Includes all measures undertaken during **manufacture** designed to ensure the uniform output of supplements that conform to established **specifications** of identity, purity, strength and other **characteristics**.

Quality Management
Coordinated activities to direct and control an **organisation** with regard to **quality**.

Quality Management System
Management system to direct and control an **organisation** with regard to **quality**.

Quality Manual
Document specifying the **quality management system** of an **organisation**.

Quality Plan
Document specifying which **procedures** and associated resources shall be applied by whom and when to a specific **product**, **process** or **contract**.

Quarantine
The status of any materials or product set aside (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 supplements.

Recall
The action taken to have a **product** returned to the **manufacturer** from the **customer**/retailer and from the final consumers. Recalls are often made due to safety concerns.

Record
Document stating results achieved or providing evidence of activities performed.

Recovery
The introduction of all or part of a previous **lot** of the required **quality** into another **lot** at a defined stage of **manufacture**.

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

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

Reprocessing
Using, in the **manufacture** of a supplement, clean, uncontaminated materials or **product** that have been previously removed from manufacturing and that have been made suitable for use in the **manufacture** of a supplement.

Requirement
Need or expectation that is stated, generally implied or obligatory.

Review
Activity undertaken to determine the suitability, adequacy and effectiveness of the subject matter to achieve established objectives.

Rework
Action on a **nonconforming product** to make it conform to the **requirements**.

Sample Matrix
The components of a sample other than the **analyte**.

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 and 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 (pre-mix) used in the production of a supplement excluding **packaging material**.

Storage Area
Designated area within the manufacturing premises where all **raw materials** and/or **quarantined material/product** and/or **finished product** can be kept safe until utilised, disposed of or distributed as applicable.

Supplier
Organisation or person that provides a **product**.

System
Set of interrelated or interacting elements.

Test
Determination of one or more characteristics according to a **procedure**.

Traceability
Ability to trace the history, application or location of **raw materials** or **product**.

Validation
Confirmation, through the provision of **objective evidence**, that the specific intended use or application of a **procedure**, **process**, equipment, material, activity or **system** leads to the expected results.

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

Warehouse
Storage area that may be located either within or away from the manufacturing premises.

Withdrawal
The action taken to have a **product** returned to the **manufacturer** from the **customer**/retailer but not from the final consumers. Withdrawals may be a voluntary action by the company.

Annex II

Hazard Analysis Critical Control Point (HACCP)

AII.1 Hazard analysis critical control point (HACCP)

HACCP is a practical technique which supplement businesses can use to help satisfy themselves and their customers that their products are safe. It achieves product safety in an efficient, reliable and cost-effective way, by focusing on hazard prevention throughout the manufacturing chain rather than relying on end-product testing.

It is a structured approach to the following:

- identifying the main risk areas in an operation;
- adopting the appropriate controls;
- ensuring the proper operation of these controls.

HACCP systems can be applied to all levels of supplement businesses, from the smallest individual operator up to sophisticated multi-national operations. The systems are designed to accommodate changes, whether in raw material supply, equipment design, processing procedures or technological developments.

Definition: A systematic approach to the identification and assessment of the hazards and risks associated with the manufacture, distribution and use of a particular product, and the definition of means for their control.

AII.2 Requirement for HACCP

There is now a greater emphasis on HACCP as an integral part of GMP within the supplement industry in some areas of the world, as companies recognise the need to critically examine the nature of the business due to their responsibility for ensuring the protection of their consumers. In certain parts of the world, e.g. the European Union, it is a legal requirement for all supplement manufacturers to have a HACCP system in place.

AII.3 Setting up a HACCP system

HACCP can only be effectively implemented once all hygiene requirements and GMP for businesses are adhered to, i.e. all controls, systems and procedures possible are in place in order to control hazards in a general way. Once this has been achieved the HACCP principles can be applied (see Figure 1). The HACCP system can be devised following the steps outlined in AII.3.1 to AII.3.13.

AII.3.1 The HACCP team

This should include key personnel from all parts of the business, e.g. a technologist, microbiologist, production manager, quality assurance manager, engineer and purchasing manager. The support and commitment of all staff is essential to the success of the exercise. The team members need to have relevant practical experience, knowledge of the products and processes within the study and suitable training in how to undertake a HACCP study and the implementation of HACCP principles. At least one member of the team should have formal HACCP training but all team members need to be trained in how to utilise the HACCP principles. The team are also responsible for ongoing review and management of the HACCP system. The management of the HACCP system and the development and implementation of the supplement safety control system remain the responsibility of the manufacturing organisation.

In the event that external expertise is sourced to assist with either the development or maintenance of the HACCP system it is critical that the management team should not delegate responsibility to the external resource. The quality of the external expertise should be formally assessed including the amount of appropriate experience in the supplement industry and the provision of appropriate references from current clients.

AII.3.2 Describe the product

This will include the identity and quantities of active and other ingredients, the structure, processing and presentation form of the supplement product, its packaging, storage and distribution conditions, required shelf life, instructions for use and any applicable microbiological or chemical criteria.

AII.3.3 Identify intended use

This will include how the consumer will normally be expected to store and consume the product and needs to give consideration to any vulnerable groups within the population.

AII.3.4 Construct production flow diagram

This should include details of all processing steps throughout the entire processing chain, from receipt of raw materials to placing the end product on the market. This information should be put into a detailed flow diagram together with adequate technical data.

AII.3.5 Verification of flow diagram

Visual inspection of the processing steps is required to ensure that they are a true representation of the processes. This verification should be carried out during normal operating hours, and the flow diagram must be amended should any deviation from the steps be noticed.

AII.3.6 List all hazards associated with each step and list any preventive measures to control hazards

A hazard is anything that can harm the consumer and can include biological, chemical and physical hazards. Preventive measures are the actions that are required to remove or reduce the hazard occurrence to an acceptable level. In certain cases a hazard analysis may show that hazards can be controlled simply by following all hygiene requirements and best practices.

AII.3.7 Determine the critical control points

Through the use of a HACCP decision tree (Figure 2), the HACCP team identifies those steps that must be controlled to eliminate each hazard or minimise its likelihood. These are the Critical Control Points (CCPs). It should be noted, however, that in certain cases, it is not possible to identify critical control points and that, in some cases, good hygienic practices can replace the monitoring of critical control points.

AII.3.8 Establish target levels and tolerances for each CCP

Target and tolerance levels need to be specified for each preventive measure, taking into account potential fluctuations within the process, in order to be able to monitor the Critical Control Point in question and ensure that critical limits, corresponding to the extreme values acceptable with regard to product safety, are not exceeded. They should be set for observable or measurable parameters, (e.g. moisture levels, pH, texture), and should be based on firm evidence that the chosen values will lead to process control. However, the requirement of establishing 'critical limits' does not imply that it is necessary to fix a numerical limit in every case.

AII.3.9 Establish a monitoring system for each CCP

This must be documented and will detect any loss of control at the Critical Control Points and provide information in time for corrective action to be taken. For each CCP, the HACCP team will decide what form of monitoring is to be done, when it is to be done and who is responsible to maintain control.

AII.3.10 Establish corrective actions

Establish what corrective action must be undertaken when monitoring identifies a deviation from a documented target level. This should include who is responsible for implementation of the action, what action is to be undertaken to correct the deviation, what action is to be undertaken with regard to products manufactured whilst the deviation occurred and a written record of measures taken indicating all relevant information.

AII.3.11 Verification of HACCP system

This will involve finished product testing, inspection of operations, audits, review of records, confirmation that CCPs are kept under control and validation of target levels etc. The verification should be carried out by someone other than the person responsible for the monitoring and corrective actions and needs to be fully documented.

AII.3.12 Establish record keeping and documentation

This requires good document control and a set procedure, (appropriate to the nature and size of the business), which will ensure that HACCP activities keep pace with any proposed changes, e.g. to ingredients, processing procedures, etc.

HACCP-related record keeping can be limited to what is essential with regard to product safety, but it must be remembered that these records need to be sufficiently adequate to provide proof of 'due diligence' to the relevant authorities should the need arise.

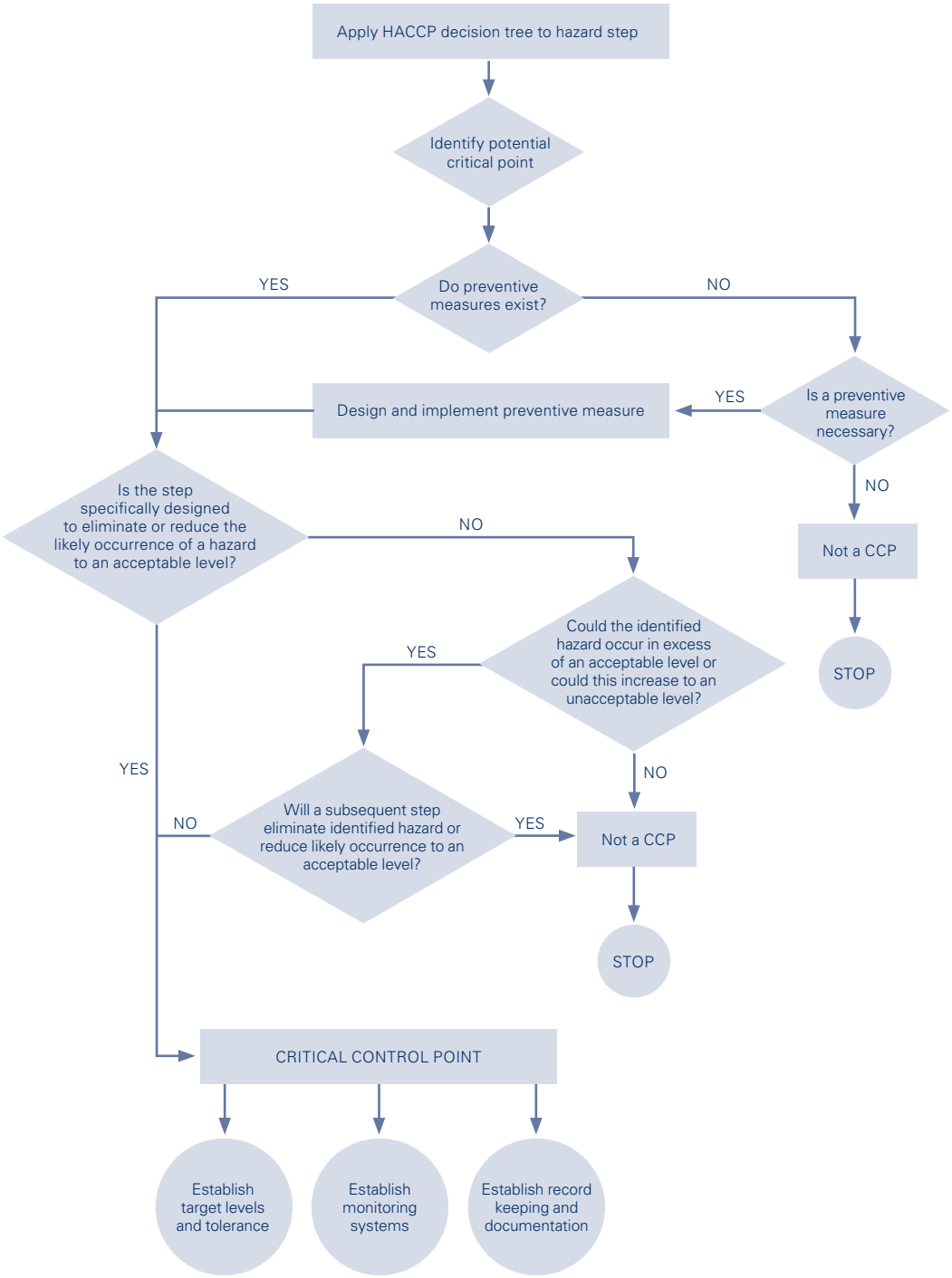
AII.3.13 Review of HACCP system

The HACCP plan should be re-assessed at least once a year to ensure it continues to provide a valid system for the identification, assessment and control of hazards and risks associated with the supplement.

Figure 1 - Seven principles of a HACCP system

1. Identify all hazards (microbial, chemical and physical) that must be prevented, eliminated or reduced to acceptable levels (hazard analysis).
2. Determine Critical Control Points (CCPs) at the points/ procedures/ operational steps at which control is essential to prevent or eliminate a hazard, or to reduce it to acceptable levels.
3. Establish critical limits (e.g. time, temperature, weight) which must be met to ensure that each CCP is under control.
4. Establish and implement an effective monitoring system for each CCP.
5. Establish the corrective action to be taken when monitoring indicates that a CCP is not under control.
6. Establish procedures, which must be carried out regularly, to confirm that steps 1 to 5 are working effectively.
7. Establish documentation, appropriate to the business size and nature, to demonstrate and record the effective application of the HACCP system.

Figure 2 - HACCP logic sequence: decision tree



Source: Codex Alimentarius Commission, 1991

Annex III

Glossary of terms associated with HACCP

Control Point
Any point, step or procedure at which microbiological, physical or chemical factors can be controlled.

Critical Control Point (CCP)
A step in a process or procedure which, if controlled, will eliminate or reduce a **hazard** to an acceptable level.

Critical Limit
A criterion which separates acceptability from unacceptability.

CCP Decision Tree
A sequence of questions to determine whether a **control point** is or is not a **CCP**.

Deviation
Failure to meet a **critical limit**.

Flow Chart/Diagram
The detailed sequence of operations involved with a particular product or process, usually from the raw material through to the end user.

HACCP Hazard Analysis Critical Control Point
A systematic and documented approach to **hazard** identification, assessment and control.

HACCP Plan
The written document which is based upon the principles of **HACCP** and which delineates the procedures to be followed to assure the control of a specific process or procedure.

Hazard
An intrinsic property of a system, operation, material or situation that could in certain circumstances cause harm to the consumer; can be microbiological, chemical or physical.

Hazard Analysis
The process of collecting and evaluating information on **hazards** and conditions leading to their presence to decide which are significant for product safety and therefore should be addressed in the plan.

Monitoring
The planned observations and measurements of targets and tolerances of **control points** to confirm that the process is under control.

Preventative Measure
Any factor that can be used to control an identified **hazard**.

Tolerance
The specified degree of latitude for a control measure which if exceeded would render the process or product unsafe.

Validation
Obtaining evidence that the elements of the **HACCP plan** are effective.

Verification
The application of methods, procedures, tests and other evaluations, in addition to monitoring to determine compliance with the **HACCP plan**.

Annex IV

Some current definitions of supplements that are in use globally

AV.1 Non-legislative definitions

Codex Alimentarius

Vitamin and mineral food supplements for the purpose of these guidelines derive their nutritional relevance primarily from the minerals and/or vitamins they contain. Vitamin and mineral food supplements are sources in concentrated forms of those nutrients alone or in combinations, marketed in forms such as capsules, tablets, powders, solutions etc., that are designed to be taken in measured small-unit quantities but are not in a conventional food form and whose purpose is to supplement the intake of vitamins and/or minerals from the normal diet.

http://www.codexalimentarius.net/download/standards/10206/cxg_055e.pdf

http://www.codexalimentarius.net/

(Accessed March 2011)

AV.2 Legislative definitions

European Union

'Food supplements' means foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32002L0046:EN:NOT

http://eur-lex.europa.eu/

(Accessed March 2011)

The Association of Southeast Asian Nations (ASEAN) (working definition)

A 'Health Supplement' means any product that is used to supplement a diet and to maintain, enhance and improve the healthy function of human body and contains one or more, or a combination of the following:

a) Vitamins, minerals, amino acids, fatty acids, enzymes, probiotics and other bioactive substances

b) Substances derived from natural sources, including animal, mineral and botanical materials in the forms of extracts, isolates, concentrates, metabolite

c) Synthetic sources of ingredients mentioned in (a) and (b) may only be used where the safety of these has been proven.

It is presented in dosage forms (to be administered) in small unit doses such as capsules, tablets, powder, liquids and it shall not include any sterile preparations (i.e. injectable, eye drops)

(Working definition correct as of March 2011)

United States of America

A dietary supplement:

- is a product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients.
- is intended for ingestion in pill, capsule, tablet, or liquid form.
- is not represented for use as a conventional food or as the sole item of a meal or diet.
- is labelled as a "dietary supplement."
- includes products such as an approved new drug, certified antibiotic, or licensed biologic that was marketed as a dietary supplement or food before approval, certification, or license (unless the Secretary of Health and Human Services waives this provision).

http://ods.od.nih.gov/About/DSHEA_Wording.aspx

http://ods.od.nih.gov/

(Accessed March 2011)

New Zealand

Meaning of dietary supplement

1) In these regulations, dietary supplement means something to which subclauses (2) to (6) apply.
2) It is an amino acid, edible substance, herb, mineral, synthetic nutrient, or vitamin.
3) It is sold by itself or in a mixture.
4) It is sold in a controlled dosage form as a liquid, powder, or tablet (which might be described on the label as a cachet, capsule, lozenge, or pastille instead of as a tablet).
5) It is intended to be ingested orally.
6) It is intended to supplement the amount of the amino acid, edible substance, herb, mineral, synthetic nutrient, or vitamin normally derived from food.

http://www.legislation.govt.nz/regulation/public/2010/0005/latest/whole.html

http://www.legislation.govt.nz/

(Accessed March 2011)

Annex V

Useful resources

Section 2

Ingredient quality/sourcing:

The Standardized Information on Dietary Ingredients (SIDITM) Protocol, Version 2.1, February 2011 (http://www.crnusa.org/SIDI/)

Section 3

Pest control:

Recommended International Code of Practice-General Principles of Food Hygiene, (section 6.3). Codex Alimentarius CAC/RCP 1-1969, Rev. 4-2003 (http://www.codexalimentarius.net/web/standard_list.jsp)

Section 4

Personnel hygiene and Infected supplement handlers:

Recommended International Code of Practice - General Principles of Food Hygiene, (section 7). Codex Alimentarius CAC/RCP 1-1969, Rev. 4-2003 (http://www.codexalimentarius.net/web/standard_list.jsp)

Section 6

Confirming reliability of supplier's test results:

The Joint SIDITM Working Group Voluntary Certificates of Analysis Guideline, Version 1.0 April 2010 (http://www.crnusa.org/SIDI/)

Section 14

Principles of Good Laboratory Practice:

Organisation for Economic Co-operation and Development (OECD) Environmental Health and Safety Publications Series on Principles of Good Laboratory Practice and Compliance Monitoring No. 1: OECD Principles of Good Laboratory Practice (as revised in 1997) (ENV/MC/CHEM(98)17) (http://www.oecd.org/)

IADSA

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Food Supplement Associations

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