Unione Italiana Food

INTEGRATORI ITALIA

GUIDELINES ON THE QUALITY OF FOOD SUPPLEMENTS

FEBRUARY 2019

Contents

PURPOSE

The purpose of this document is to provide *specific* Guidelines for the food supplement manufacturing sector that cover the entire production and quality control cycle: from the purchase of materials through the development, production, packaging and storage phases to the distribution or release of the finished product.

As far as possible, each operator involved in any phase of the production and/or distribution cycle should adopt such guidelines for the parts within its remit.

CHAPTER I

- General Part -

INTRODUCTION

Food supplements, as defined in Directive 2002/46/EC of 10 June 2002 as adopted nationally by Legislative Decree no. 169 of 21 May 2004, are "*foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances, such as vitamins and minerals, or other substances with a nutritional or physiological effect, in particular but not exclusively amino acids, essential fatty acids, fibres and extracts of vegetable origin, whether alone or in combination, in pre-dosed form, namely forms such as capsules, pastilles, tablets, pills, chewing gum or similar, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders*".

Food supplements to be marketed in EU States must meet both specific criteria regarding composition, production, labelling and marketing set out in Directive 2002/46/EC on food supplements and any additional national provisions and all cross-European legislation on food safety, hygiene and sanitary regulations for food production, with the related GMP based criteria, and consumer information.

It should, however, be emphasised that, as regards foods for general consumption, food supplements are meant to provide micro-nutrients and/or other substances having a nutritional or physiological effect in pre-determined quantities and in particular forms of dosage; therefore, their development and production requires specialist skills and operating measures peculiar to the sector.

STRUCTURES, PREMISES AND EQUIPMENT

As defined in article 10 of Legislative Decree 111/92, amended with Legislative Decree 152/2012, the production and packaging of food supplements must be carried out in establishments authorised by the Italian Ministry of Health. Authorisation requires prior confirmation of the existence of the hygiene conditions and technical requirements laid down by (EC) Regulations 852/2004 and 853/2004 on foodstuff hygiene and by the Ministerial Decree of 23 February 2006 regarding the technical requirements and general criteria for licensing the production and packaging of food supplements, as well as the availability of a suitable laboratory for product control.

Production flow and business layout

The business shall first of all prepare a plan of the establishment that clearly identifies:

- Processing zones
- Access points for personnel
- Access points for raw materials and packaging
- Routes for personnel movement
- Routes for movement of raw materials
- Waste flow
- Production flow
- Position of areas for personnel, toilets, canteens etc…

The raw material, packaging, product and waste movement phases shall not in any way compromise the safety of the food supplements manufactured. The process flow shall be managed in a way that minimises any possible contamination of raw materials, semi-finished products, packaging and finished products. The business premises shall have sufficient space to allow employees to work in optimal conditions so that all the operations are also carried out in suitable hygienic conditions.

Structure of the building

Warehousing requirements

In accordance with national legislation, warehouses for storing raw materials and food supplements, as well as packaging materials, shall be distinct and separate, arranged sequentially to the production flow and used solely for the purpose for which they have been designed. In addition, they shall be sufficiently large, easy to clean and fitted with suitable equipment so that all the goods can be arranged in an orderly manner and in the right temperature and humidity conditions. In the case of small-size establishments with limited production activities, it is permitted to keep both the raw materials and packaging and finished products in the same area provided that they are arranged according to rational distribution criteria and in compliance with hygiene rules specified at community level.

Areas designated for movement of raw materials, production and packaging

According to the general hygiene requirements, the conditions set out in annexe II of EC Regulation 852/2004 apply

It is, therefore, necessary for the walls forming the entire structure to be maintained so as to avoid dust build-up and to be structured so as to facilitate the cleaning operations. The floors shall be kept in a good condition and shall be easily washable. If a drainage system is present, this shall be located and maintained in order to reduce the risk of product contamination and not compromise product safety. Ceilings shall be designed so that cleaning operations can be carried out easily and also prevent any risks of contamination for supplements, raw materials and packaging. In the case of windows or glazing, these shall be properly screened to prevent the entry of animal pests. If these are made of glass, they shall also be properly protected against breakage.

The external doors shall fit snugly on the loading ramps, or special protections shall be installed to ensure they fit properly. The doors giving access to the areas designated for food supplement production shall always be kept closed during periods of activity. In any case, suitable precautions shall be taken to handle any entry of pests.

Adequate ventilation and a suitable exchange of air shall be assured in premises used to store products in general, in order to prevent condensation forming.

If there are internal laboratories, the premises used to carry out chemical-physical and microbiological analyses shall necessarily be separated. Any laboratory shall also be fitted with all the equipment required to carry out the declared analyses, in accordance with current legislation.

The food supplement production and packaging lines may not be used for purposes other than the manufacture of foodstuffs. In this case, before a food supplement is produced, the plant to be used for its production shall be properly sanitised in accordance with the certified cleaning procedures, so that any residues from previous processes are eliminated. As far as storage and warehousing premises are concerned, properly demarcated areas shall be provided for storing raw materials and finished products involved in the various productions.

Structures for personnel

Special changing rooms shall be provided for employees and for anyone entering the business (visitors or contractors); these shall be positioned so as to allow direct access to production, without crossing through external areas; otherwise, a special risk assessment shall be prepared. A sufficient number of lockers shall be provided inside the changing rooms, based on the number of employees, and shall be provided with separate compartments, so that normal clothes and personal items can be kept separate from standard work apparel.

Services

The water used for all the activities, from production to hand washing and for cleaning equipment and plant, shall be supplied in sufficient quantities, be potable and not be subject to any source of contamination, in accordance with current legislation. Water quality, both from the chemical and the microbiological point of view, shall be monitored through special analyses at least once a year. The sampling points shall be clearly indicated in the plan layout and the points at which samples are taken and frequencies shall be established in accordance with the risk analysis.

The use of non-potable water is permitted only and exclusively for:

- fire-prevention control;
- steam production;
- refrigeration;
- toilet flushing or other similar purposes.

Non-potable water shall circulate in a separate and clearly identified system and shall not in any way be connected or enter systems provided for potable water circulation.

Where gas, air or steam is used in direct contact with the products, these shall be monitored constantly to prevent any risks of contamination.

Equipment

All the equipment used shall be constructed with suitable materials and be such as to allow the sanitisation procedures to be executed correctly. It shall also comply with the pertinent legal requirements.

All equipment shall be designed and arranged in a way as to protect the products against external contamination such as drips of lubricant and similar.

It shall:

- be safe and be quick to inspect and dismantle;
- before each use, allow a check to be carried out that it is clean and sound;
- be clean and repaired immediately after use or any faults.

If equipment requires lubrication, only food-type certified lubricant shall be used.

Maintenance

The company shall provide a documented scheduled maintenance system covering all plant and process equipment. In addition to the aforementioned programmes, the company shall ensure the implementation of extraordinary maintenance operations where there is a risk of contamination by foreign bodies caused by equipment damage. These operations shall be properly recorded.

Maintenance work shall be followed by a suitably documented hygiene check.

The calibration of all the measurement equipment (weight, volume, temperature, etc.) shall be carried out using suitable standards and in accordance with current legislation.

A detailed record of calibrations shall be kept. These shall be regularly checked to ensure that the calibration is updated correctly and that the equipment works according to the precision standards required.

Instruments subject to regular calibration should be protected against any accidental impact. All work carried out on such equipment should:

- be carried out only by authorised and properly trained personnel;
- follow the prescribed procedures;
- be formally recorded in the special register for each item of equipment.

PERSONNEL

People and their activities play a key role as possible sources of food contamination. Preventive actions in the field of personnel hygiene, apparel and behaviour are hence essential if the risk of contamination is to be reduced.

Personnel involved directly in the production process phases shall be regularly involved in training, development and awareness processes and shall meet the hygiene requirements specified in the "Hygiene Package" or (EC) Regulation 852/2004.

All personnel shall be made aware of their own role and responsibility on the matter of health, safety and current legislation.

In fact, the business shall ensure that personnel employed on duties that could have a direct impact on product safety, legality and quality are fully able to cover the role assigned and that such competence has been acquired through training courses and work experience or verified by a specific certificate of qualification for the duty assigned.

The "Quality Control Supervisor"

The 23 February 2006 Decree on the technical requirements and general criteria for licensing the production and packaging of foodstuffs specifically states that every establishment shall appoint a *"Quality Control Supervisor"* for the production process who may otherwise be identified as the Quality Assurance Supervisor.

This person shall possess a degree in Biology, Chemistry, Pharmaceutical Chemistry and Technology, Pharmacy, Medicine, Food Sciences and Technologies or equivalent.

He/she shall, in particular, ensure:

- product safety and quality;
- the elaboration and continual updating of auto-control plans defined considering the specific nature of food supplement production and packaging and the specific nature of the ingredients used;
- oversight of the correct application of the auto-control plans;
- compliance with the hygiene rules defined for food supplement production and packaging;
- the application of defined procedures for the purchase, acceptance and traceability of raw materials and packaging materials;
- the hygiene of all business structures connected with the production, packaging and storage of food supplements and their ingredients and packaging;

- the efficiency of the establishment's structures to ensure the safety and quality of the food supplements produced and packaged;
- the preparation and keeping of production records indicating the date and time of individual processes;
- notification to the competent local Health Authority and the owner of the establishment of any irregularities, any substantial change to the production or packaging structures and changes in the analyses carried out in the internal laboratory.

Training

Food supplement producers are responsible for identifying the measures necessary for their operations. These measures shall ensure that all potential employees, including supervisors, managers and any seasonal workers, have the necessary information for performing their roles in order to safeguard consumer health.

"Food hygiene" regulation requires all the staff involved to be properly trained and informed about hygiene matters based on their own working activity.

Specific training for each employee shall cover in particular:

- the employee's specific role;
- good manufacturing practices (GMP);
- importance of personal hygiene and related factors;
- principles of the HACCP system.

Every new employee shall be properly trained and instructed before starting to perform his/her specific duties. Such training shall be regular and, if necessary, changed or extended depending on requirements. At the end of the session the person's understanding of the training shall be assessed.

Appropriate GMP training shall also be provided to all those employees who may enter the production areas or activities related thereto in an administrative capacity, for maintenance and cleaning purposes and as external personnel.

(Internal staff or external advisors, involved in training staff in production duties and managing GMP-related internal and external audits, shall be trained according to a recognised national standard where applicable).

Appropriate training shall be planned and recorded for each employee.

The supervision, instruction and training shall necessarily be correlated with the work carried out by the operators themselves, the surrounding environment and the risks related to product safety arising from their activities. Considering all the risks that may arise, the businesses shall consider:

- the nature of the product;
- the way in which operators work on the product;
- the type of process and related risks.

Hygiene rules

Hygiene and conduct standards shall be developed, documented and observed by all personnel, including apprentices and interns, contractors and visitors in order to reduce the risk of product contamination.

Production unit personnel, as well as circulating personnel, shall maintain a high level of hygiene, use apparel suitable for the standard of production (clean and washable and use of hair covering, gloves or beard mask where required) and make sure it is worn correctly.

Personnel shall always wash their hands, particularly when starting to handle food, straight after using the WC, after handling any material that could be a source of contamination and whenever resuming production activities.

Nails shall be kept short, clean, in a suitable state and not be varnished. False nails are not permitted.

If the business allows operators to work with cuts, superficial wounds or grazes, these should be covered with a suitable coloured waterproof dressing and/or easily visible plasters that can be detected by a metal detector. The employee is responsible for notifying the employer in the event of this kind of injury and for checking the number of plasters used. Loss of any plaster during working activity shall be reported promptly and procedures to find it shall start as soon as possible.

Rules of conduct

Personnel shall comply with the rules of conduct suitable for production considered to be hygienic, and, in particular, there shall be absolutely no spitting, smoking or use of chewing gum in any of the production areas and attention shall also be paid not to sneeze and cough over the raw materials and semi-finished and finished products.

Food and beverages and medicines shall be kept, consumed and taken in the designated areas only.

Personal effects such as necklaces, except for wedding rings, watches, piercings and other items including purses and wallets, shall not be worn or taken into food handling areas.

The use of cosmetics and perfumes, after shave and makeup shall not be excessive and in any event such as to represent a risk. It is not permitted to use false nails and eyelasches.
Waste shall be disposed of in the special containers and the workplace and workstation shall be kept clean and tidy.
The compartmentalisation, zoning and production flows envisaged shall always be respected so as not to impact negatively on product safety and hygiene criteria.

State of health

Personnel affected/healthy carriers of any disease should report their own state of health to their direct superior and should not be allowed in the production areas.
People who resume work after an infectious illness or after coming into contact with people who are probably infected, shall inform the local health authority before resuming work.
The conditions that shall be reported promptly are:

- jaundice
- diarrhoea
- vomiting
- fever
- flu symptoms such as sore threat and temperature
- visibly infected skin injuries (blisters, cuts, etc.)
- secretions from ears, eyes and/or nose

Visitors and temporary personnel

In production areas visitors and temporary personnel shall:

- wear protective clothing suitable for the production standard adopted by the business;
- inform business supervisors of their own state of health (e.g. infections, infectious diseases, etc.)
- be informed about current rules of hygiene.

PRODUCT DEVELOPMENT

Quality is a holistic concept that must be pursued and built from the very first phases of product development. Scientific, technical and regulatory criteria are equally important and fundamental for developing a successful food supplement.

Scientific criteria

The choice of nutrients and substances having a nutritional or physiological effect and the related dosages shall first and foremost be consistent with:

- the pre-set nutritional or physiological objective;
- population group at which the supplement is addressed.

Any negative interactions between components, as well as additive or synergic effects that could have an impact on the product's efficacy or safe use, shall be kept under due consideration.

Technical criteria

A fundamental aspect of food supplement design lies with the prior assessment of all factors that could affect the stability of the proposed formula and, as a result, the coherence with the quantities of substances to be shown on the label (see SHELF-LIFE AND STABILITY chapter).

The aim of the product's overall composition, and the packaging used, and the processes chosen for its development shall be such as to define a commercially viable shelf-life. The requisite measures may include, amongst other things:

- use of micro-encapsulated ingredients to minimise the interactions with the environment and/or the other product components
- use of preservatives or antioxidants
- resorting to suitable overdosages; this technique is very well-established and used to compensate for changes in the degradation kinetics of certain substances (e.g.: vitamins, etc.) during the product's shelf-life and to ensure compliance with the values declared on the label
- identification of forms of dosage most compatible with the formula established
- identification of the most appropriate packaging material for product conservation (barrier against light/oxygen/humidity)
- definition of 'in process' controls (e.g.: humidity content, etc.)

- adoption of controlled temperature and humidity conditions
- modified atmosphere packaging
- inclusion on the label of specific product conservation methods
- etc.

Regulatory criteria

It should be stressed that any design proposal that has defined its main objectives and the technical criteria required to produce a quality product has to be elaborated in the context of applicable legislation and taking account of any risks associated with the type of product and/or production processes identified for its production. If such steps are not taken from the very start of the design phases, even applying the most rigorous GMPs could result to be inadequate for purposes of product quality, safety and legality.

The following aspects are to be verified based on current legislation. It is, thus, fundamental to constantly monitor industry legislation and evaluate the potential impact of each new provision on the activities related to product development or reformulation.

Requirements for ingredients

All the ingredients used shall comply with the food safety requirements applicable. The following, in particular, are to be verified:

- identity, nature and any qualitative-quantitative composition (supports, additives);
- conformity with the chemical and microbiological purity criteria established in order of priority by: applicable food legislation; universally accepted standards; internal specifications based on the evaluation of the type of ingredient and the risks that may be associated thereto;
- where applicable, conformity of the starting ingredients and/or materials with current legislation concerning BSE/TSE, pharmacologically active substances, chemical and microbiological contaminants, pesticides, extraction solvents, radioactivity. If given requisites apply to the finished product it is desirable to obtain from suppliers suitable guarantees regarding the “at risk” ingredients;
- any sources of allergens.

Packaging material requirements

Packaging materials shall meet the legal requirements applicable; in any case they shall not transfer substances into the product that could create a hazard for consumer health, cause unacceptable

changes to the product's composition or alter its organoleptic characteristics. The following are to be verified in particular:

- conformity with European legislation, any national regulations and scientifically recognised guidelines for materials and items in contact with food (primary packaging);
- conformity with the heavy metal limits established by the European directive on packaging and packaging waste;
- composition, technical and quality specifications;

It should be remembered that the size of the packs presented to the consumer shall not be misleading about their content (size suitable for the actual content).

Legality of ingredients and final composition

Both the ingredients used and the product's overall composition shall comply with the European and national legislation applicable. In particular:

- flavourings shall comply with (EC) Regulation 1334/2008; they shall not contain substances that preclude their use in food supplements; any restricted substances are to be carefully assessed.
- additives shall comply with (EC) Regulation 1333/2008; their use in the finished product shall comply with any maximum levels established for the category of supplement under development (17.1, 17.2, 17.3) and conform to the purity criteria for food additives in compliance with Reg. 231/2012.
- only the vitamins, minerals and related sources listed in Directive 2002/46/EC are permitted.
- the quantities of vitamins and minerals shall comply with any maximum levels established and be consistent with the design proposals (e.g.: intended use).
- other ingredients having a nutritional or physiological purpose and related quantities are permitted in the country where they are marketed and are consistent with the design proposals (e.g.: plausibility of the effect, intended use).
- any novel food ingredients (NFI) shall be authorised for use in food supplements and used under the conditions specified in the respective authorisation decisions.
- any starting GM ingredients or materials shall be authorised and correctly labelled.
- any ingredients treated with ionising radiations shall be authorised and correctly labelled.
- additives in: additives, flavourings and nutrients are permitted therein or in the finished product; in this latter case, they shall comply with any usage restrictions in the finished product and be correctly labelled.

- any overdosages of micronutrients required to guarantee the shelf-life assigned to the product shall be calibrated in accordance with the tolerances established by the European Commission's 2012 guidelines as applicable (e.g.: declared quantities; nutritional or health-related claims).
- product composition and/or application do not infringe any patents.

Genetically modified organisms

The raw materials shall conform to European legislation, on the matter of Genetically Modified Organisms (GMOs).
The laws applicable to this subject set out the rules relating to the ways in which genetically modified organisms (GMOs) are authorised and overseen, as well as the labelling of foodstuffs and genetically modified animal feed.

Traceability

All the food ingredients, and hence also the ingredients used in food supplements, shall conform to the traceability requirements laid down by European legislation.
Each operator in the sector involved in the ingredient/plant preparation production and distribution process shall be able to identify all the suppliers upstream and all the users downstream so as to ensure full traceability right along the supply chain.
Information on traceability shall be conserved for a suitable period (e.g.: shelf-life of the ingredient/plant preparation or the finished product plus one year) and shall be made available to the competent Authorities if requested.
Food supplements containing ingredients/plant preparations placed on the market shall be properly labelled and identified to allow their traceability.

Labelling

Information on the label is in Italian and conforms with the applicable rules on labelling:

- general provisions laid down by (EU) Regulation 1169/2011 on information to the consumer;
- additional provisions or provisions derogating from (EU) Regulation 1169/2011 as established by Directive 2002/46/EC on food supplements and by any national rules/guidelines;
- obligatory case-specific information as laid down by other European regulations or national provisions having an impact on labelling (GMOs, irradiation, additives, claims, NFI authorisation decisions, etc.).

It should be stressed that the food supplement nutritional table does not indicate the 'big 8' pursuant to (EU) Regulation 1169/2011 but merely the quantities of nutrients and substances having a nutritional or physiological effect expressed in terms of recommended daily dose. The declared values refer to the quantities guaranteed up to the end of the shelf-life as determined analytically by the producer. The pertinent tolerance intervals apply to the micronutrient-related values. Variances from these intervals, which may be recorded during the official control, are to be justified (e.g.: maximum daily levels permitted locally vs scientifically recognised tolerable levels).
If applicable, micronutrients are also expressed as a % of reference intake. The preferential use of the VNR or RI acronyms is to be verified in the country where the product is to be marketed.

Voluntary information

Without prejudice to the legal requirements in the field of communication and the recommendations of Advertising Self-Regulation Institutes,

- any voluntary information shall comply with the general principles of fair information practices (art. 7 of (EU) regulation 1169/2011);
- any references to nutritional effects and health shall comply with the general provisions and specific usage conditions established by legislation on nutritional and health claims;
- any references to the product's suitability for particular groups of the population shall be scientifically well-founded and comply with the provisions laid down by European legislation (e.g.: gluten-free) or by the local regulations in the country where the product is to be marketed (e.g.: lactose-free).

Technical checks

Appropriate checks (laboratory tests/pilot lot) consistent with the criticalities of the processes applied must be carried out to assess the formulation's feasibility from the technological standpoint. Such checks also include the suitability of the environmental conditions throughout the production process as well as the primary packaging's integrity and seal.

SHELF-LIFE AND STABILITY

Shelf-life

Food supplements are intended to provide micronutrients and/or other substances having a nutritional and physiological effect in pre-determined quantities and in pre-dosed forms. The qualitative-quantitative specifications of all nutrients and substances having a nutritional or physiological effect shall be guaranteed and the physical and organoleptic characteristics shall remain unchanged throughout the product's shelf-life, or up to the end of the minimum durability (use by date or "best before") indicated on the label.

It is important to stress that product stability is fundamental not only to ensure its quality, but also to meet requirements and satisfy consumer expectations. There are multiple factors that can influence product stability, including:

- ambient conditions (temperature, humidity, oxygen, light, …);
- intrinsic characteristics of substances (inertia *vs* reactivity to ambient conditions, resistance *vs* susceptibility to microbial growth, etc.);
- any interactions between components;
- state and physical characteristics of the product (liquid *vs* solid; grain size, etc.);
- characteristics of the packaging material (spectral transmittance; permeability to oxygen and aqueous vapour; size in relation to occupied volume [head space], etc.).

These variables must be properly assessed as early as the product design stage, so that all steps can be taken to develop a plausibly stable formula compatible with the shelf lives required by the market (cfr.: "Product development" chapter).

The assignment of the correct use by date ("best before") shall take account of all the available information, which can be obtained from:

- data obtained from specific stability studies conducted on the product;
- extrapolation of data obtained from stability studies on products similar in terms of matrix and combination of ingredients;
- data from scientific literature regarding the stability of individual ingredients;
- stability data received from raw material producers.

Stability

Stability studies aim to attribute a period of validity to products under development, check the suitability of the packaging material proposed, assess any interactions between the components not expected during the formulation phase and identify the right storage conditions for the product.

Long-term studies

The ideal approach for attributing a correct shelf-life is to run real-time studies for a period equal to or exceeding the period of validity proposed.
The tests under controlled temperature and humidity conditions are carried out with the formulation in the primary packaging planned for marketing, at temperatures and relative humidity percentages representative of the climate area of the country in which the product is to be marketed. The samples are stored for the period specified in the stability protocol in heaters where both temperature and relative humidity are controlled.
To standardise as far as possible the sample storage conditions for performing long-term studies in different countries, it has been proposed that the world be subdivided into different climate zones based on the annual average thermo-hygrometric conditions in the various nations. This approach has been commonly accepted and included in the regulatory guidelines and in the Pharmacopoeia of various nations and has become the standard for developing and placing new drugs on the market.

The 5 different climate zones identified, with the related long-term storage conditions for executing stability studies, are:

- Zone I: Temperate climate: 21°C / 45% R.H.
- Zone II: Sub-tropical and Mediterranean climate: 25°C / 60% R.U.
- Zone III: Warm dry climate: 30°C / 35% R.U.
- Zone IVA: Warm humid climate: 30°C / 65% R.H.
- Zone IVB: Warm and very humid climate: 30°C / 75% R.H.

The ICH (The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) has issued special guidelines providing information on executing studies in the various climate zones.

In the nutraceutical sector inspiration has often been drawn from the ICH for organising stability studies; these guidelines are a valuable point of reference but should not be considered binding.

Accelerated studies

When, for commercial reasons, the launch of the product is not compatible with the timescales of a stability check in normal conditions, studies in stressful conditions (accelerated stability) are used on a preliminary basis, provided that they are not known to be incompatible with the product type (e.g.: probiotics – see Guidelines for the quality of Probiotic-based Food Supplements).

These short-term studies are conducted at high temperature and humidity, so as to increase the speed of the chemical and physical degradation processes, supplement data obtained from long-term studies and analyse the effect of any temperature and/or humidity excursions, which may occur during the distribution chain.

For the accelerated stability tests the samples are generally stored at 40°C ± 2°C / 75% RH ± 5% RH or at 30°C ± 2°C / 65% RH ± 5% RH, depending on product characteristics; for those requiring storage in a fridge, the study is carried out at 25°C ± 2°C / 60% RH ± 5% RH.

Intermediate conditions may be adopted if the accelerated study fails.

Sometimes it may be useful to carry out preliminary studies of interactions between components in stressful conditions during the formulation phase, in order to identify any incompatibilities.

If potential criticalities in a formulation are already known or can be assumed, it is advisable to assess in parallel different packaging materials, offering a different level of protection against those factors (humidity, oxygen, …) that could compromise their stability.

Frequency of controls and choice of parameters to be monitored

For the long-term studies the controls are generally planned at quarterly or six-monthly intervals, for a period of time no shorter that the period of validity proposed, whilst for those carried out in accelerated conditions the controls may be closer together and, in any event, last for a shorter time overall.

To plan the controls correctly, choose the parameters to be monitored and then interpret the data, an assessment must be made of the nature of the product and ingredients, the claims to be made on the label and the storage conditions envisaged, also considering the fact that when a product contains several active components, these may degrade at different rates.

Parameters that are generally monitored:

- organoleptic characteristics (colour, odour, flavour, …)

- physical characteristics (e.g.: humidity; fluidity and solubility of powders and granulates; hardness, friability and disaggregation time of tablets; viscosity and pH of semi-solid or liquid products, …)
- microbiological parameters (e.g.: total aerobic count, moulds and yeasts, absence of pathogens, …)
- quantities of "active" constituents declared on the label or, primarily for highly complex matrices for which the analytical methods do not offer sufficient sensitivity/specificity, of constituents that are less stable or in any event reasonably predictive of the product's overall stability.

Data analysis

At the end of the scheduled controls the results shall be assessed overall, in order to confirm the shelf-life originally proposed or not.

It is important to emphasise that the results achieved in the accelerated studies are not always predictive; in fact, it may be that reactions or interactions that occur in particular thermo-hygrometric conditions do not occur in standard storage conditions, and so it is often experience that helps to understand and interpret the data.

In the case of active constituents that degrade over time, it is established practice to increase their quantity over the quantity declared on the nutritional label; this overdosage means that the product specifications can be assured up to the end of the period of validity.

STORAGE: RAW MATERIALS, INTERMEDIATES, FINISHED PRODUCTS

Storage areas shall be identified and segregated from production areas and shall be designed and managed so that various categories of materials and products are stored correctly:

- raw materials,
- packaging materials,
- production intermediates,
- bulk products,
- finished products,
- products in a state of quarantine,
- rejected products,
- products returned by the market or subject to the recall procedure.

The following minimum requirements shall be satisfied:

1. Sufficient space to ensure the orderly storage of each component, avoid damage to goods during handling or cases of accidental mix-up.
2. Adequate state of cleanliness: a cleaning plan shall be provided in accordance with specific procedures. Cleaning operations shall be documented in the same way as the post-intervention inspections or the periodic inspections to check that the area is in a good condition.
3. Presence of a reception area separate from the storage areas, in which the goods are stored and subject to the due goods inwards controls.
4. Presence of a despatch area in which the goods shall be controlled before loading onto the transport vehicle.
5. Presence of an area for materials in quarantine. The quarantine status of the materials may be managed through physical segregation or through other systems for which proof of equal efficacy shall be provided.
6. Presence of an area for materials rejected or subject to the recall procedure: this shall be suitably segregated, and the status of the materials stored therein shall be identified.
7. Specific rules shall be identified for storing allergens and material in a liquid state with the purpose of avoiding accidental contaminations of other materials.

8. If provided, the materials sampling or inspection zone shall be segregated and managed in accordance with particular procedures designed to prevent accidental contamination, cross contamination and mix up.
9. The zone outside the stores designated for unloading/loading the transport vehicle shall be suitably protected (canopies, inner doors) so as to prevent possible contaminations from the outdoor environment.
10. Access to storage areas shall be reserved for authorised personnel.
11. A Pest Control Plan shall be provided with the aim of preventing or reducing the danger of contamination. Traps shall be positioned in the critical points, identified, mapped and checked regularly. The results of the monitoring activity shall be re-processed.
12. Temperatures shall be monitored and/or controlled, and limits set that are compatible with the nature of the stored goods. It is recommended that the storage area be mapped so as to confirm that the ambient temperature is uniform. When particular temperature and/or humidity conditions are required, suitable storage areas must be identified, and the ambient conditions monitored.
13. Lighting shall be sufficient to be able to locate and identify the materials and facilitate the structure's cleaning and maintenance operations.
14. Adequate measures shall be put in place to protect the materials from direct exposure to ultraviolet light.
15. The characteristics of pallets shall be such as not to be a source of further goods contamination (e.g. HT pallets).
16. The expiry dates shall be managed, and specific systems shall guarantee against the accidental use of out of date materials.
17. All materials shall be uniquely identified (code/lot) to ensure their traceability. In particular, effective systems shall be adopted to identify allergens. Materials shall also be protected by sound packaging free of foreign bodies.
18. The activities involved in receiving, storing and turnover of materials shall be coded in business procedures approved by authorised personnel.

PRODUCTION AND PACKAGING

(EC) Regulation 852/2004 provides for the generalised application of permanent procedures to control potential hazards, and based on HACCP system principles, as an auto-control methodology for all production operations except for primary production.
The purpose of the HACCP system is to base the product warranties on prevention instead of on finished product controls alone. This system should be structured in a consistent manner with the specific business situation but should be kept constantly up to date and integrated with the results of the activities involved in supervision/verification/corrective actions.

In general principle, all material handling operations (receipt, storage preparation, production, packaging, labelling) shall be conducted in accordance with specific procedures.
Specific procedures shall exist for each phase of the production cycle designed to ensure that the operations carried out meet the standards set. This documentation shall be clear, unambiguous, drawn up by the competent business functions and approved by the Quality Assurance supervisor.
All the operations shall be recorded when they are executed in appropriate approved documentation (Batch Record).
Any deviation from existing procedures shall be approved, documented and justified by the functions involved.
Production shall be supervised by competent personnel.
Access to the production areas shall be restricted to authorised personnel only.

Technical and organisational aspects

The equipment, premises or main lines used shall be identified in the production lot fabrication documents along with the name of the product previously processed on the line and the cleaning operations.
The risk of contamination/cross-contamination of the product or raw materials shall be prevented by keeping under control accidental releases of materials foreign to the process by other materials, equipment or personnel. The gravity of the risk shall be taken into consideration based on the nature of the contaminant and contaminated product.
When pertinent and where possible, provision shall be made for the following preventive measures regarding the organisational and technical aspect:

- dedicated areas, isolation of certain equipment and air treatment systems;

- production equipment designed so as to limit the risk of cross-contamination during processing, cleaning and maintenance;
- use of closed containment systems during the transfer of materials and products or product protection systems;
- use of physical containment barriers;
- dust removal systems close to the source of the contaminant;
- where possible, use of single-use tools;
- definition of appropriate pressure gradients with the aim of containing the contaminant in the specific area;
- adoption of suitable recirculation air treatments;
- adoption of "in place" cleaning systems or, alternatively, use of separate areas for dirty and clean equipment in the washing areas;
- adoption of detailed washing instructions for plant and production areas;
- validation of effectiveness of cleaning procedures;
- adoption of adequate dress procedures to protect the product against contamination in the exposure areas;
- definition of procedures for managing deviations (e.g.: spills, etc.).

Access to production areas shall be restricted to authorised personnel only.

Activities and conduct in the production environments shall be supervised by competent personnel.

Suppliers and materials inwards

The selection, qualification and approval of suppliers shall be documented in the quality system of the business (see chapter: "QUALIFICATION OF SUPPLIERS").

The quality requisites demanded by the producer shall be discussed beforehand and agreed with the supplier.

For each consignment of material, a check shall be made that the containers are intact, match the despatch and order documents and labelling. These checks shall be documented.

Each lot shall be subject to sampling, the identification procedure and, where required, particular chemical/physical/microbiological/technological controls to confirm that it complies with the technical specifications and food safety requirements specified in the HACCP plan. Reference is made to the "QUALITY CONTROL" chapter for further details.

In the storage areas all the components in all their containers, including non-original, shall be labelled and uniquely identified using a code number, description, lot, quantity and by their status (approved, quarantine, rejected). Where pertinent, the expiry date shall be indicated. The status of the material may be managed using IT tools.

All the containers shall be in a suitable state of cleanliness.

The raw materials may be used only if the component/lot is within its period of validity and only if it has been identified and released (APPROVED status) by Quality Control following:

- verification of the supplier's certificate (only if the supplier is validated);
- sampling and analysis in accordance with specifications and approved methods;
- results conforming to the defined specifications and the limits imposed by the HACCP risk analysis.

Each ingredient shall be dispensed in accordance with the quantities prescribed by the fabrication formula and specific procedures.

The weighing operations shall be supervised and, where possible, also conducted with systems that ensure that the correct quantities are dispensed and added.

Special recording documents shall be designed and maintained to ensure the traceability of all material leaving the supplier up to the finished product lots in which the material has been used.

The containers of raw materials dispensed (original containers or new containers) shall have an identification label (code lot description) and the reference to the weighed quantity.

Process phase

Before starting any production process, it is necessary to ensure that the work area and plant are clean and uncluttered by any material extraneous to the processing. This control must be documented.

Bulk products shall be stored in the appropriate conditions (e.g.: temperature, humidity, modified atmosphere).

Where necessary, process controls and controls of ambient conditions shall be carried out and recorded.

Packaging phase

Each item of packaging material shall also be identified by a revision number or number identifying the print version.

All obsolete material shall be properly segregated, and its destruction documented.

Before starting any production process, it is necessary to ensure that the work area/packaging line are clean and free of any product, material or documents extraneous to the processing. This control shall be documented and guided by a check list.

The processing procedures and flows of materials shall be such as to minimise the risk of materials getting mixed up and cross-contamination of the product with foreign substances. The processing shall hence be physically segregated.

Confirmation shall be given that the materials to be used are correct in relation to the packaging instructions.

Where applicable, preventive control activities shall be put in place to detect possible physical contaminations (metal, foreign bodies).

The primary packaging activity shall be followed by the container labelling phase in accordance with procedures designed to minimise the risk of incorrect labelling or mix-up.

All the automatic control mechanisms shall be checked regularly to test they are working properly. The results are to be recorded.

All variable data shall be clearly legible and difficult to erase.

Specific process controls, carried out and recorded regularly, shall concern:

- the variable data print phase (lot number, expiry date);
- general appearance of the product;
- completeness of the packaging phase;
- correctness of materials in relation to specifications.

All the samples used to carry out the process controls shall be eliminated.

All units involved in an accidental event may be reintroduced into the process only after careful inspection, investigation and approval by authorised personnel. These non-routine events shall be tracked in the quality system.

Counter-samples of finished product shall be taken in sufficient quantities for at least two complete repeat analyses. The taking of samples shall be recorded in the fabrication documents.

The finished product shall be kept in quarantine status and may be released after the samples and the fabrication documentation have been assessed. The release shall be carried out by qualified personnel.

Yield

Where applicable, the process yield shall be calculated at the end of each production phase. The calculations shall be carried out by an operator and checked by a second operator working independently from the first one to record any discrepancy outside the limits.
Any deviation from yield limits shall be discussed and investigated.

QUALITY CONTROL

Quality Control oversees:

- sampling
- definition of specifications
- analyses
- definition of all procedures and documents ensuring that the necessary tests are carried out
- release of materials: Quality Control ensures that materials and finished products are released for use only if their quality is judged to be satisfactory.

The responsibility of the head of quality control and the production supervisor shall be properly defined and separate so that the product acceptability assessment can be given in an authoritative and independent manner.

The minimum quality control requirements are as follows:

- Structures, premises fit for purpose;
- Analytical instruments fit for purpose, set and calibrated in accordance with a defined approved plan;
- Specific procedures for using and cleaning analytical tools shall be available;
- Where applicable, preliminary functionality and performance tests shall be carried out on the analytical instrument before it is used. Maintenance, calibration, setting and challenge of analytical instrumentation shall be recorded as shall its use;
- A sufficient number of suitably trained personnel to carry out their respective activities;
- Presence of procedures and/or approved methods for sampling and testing of raw materials, packaging materials, intermediates, bulk products, finished products and monitoring of ambient conditions having an impact on product quality.

The sampling shall be carried out by authorised personnel in accordance with procedures approved by quality control.
The sampling and testing activity shall be properly recorded so as to provide proof about the correct application of procedures and any deviation from approved procedures shall be investigated and recorded.
The results of the inspection and analysis activity shall be assessed against approved specifications.
The finished product conformity assessment shall also cover the production documentation

(manufacturing and packaging) and any deviations from the approved procedures. The finished product may be released subject to formal authorisation by the Quality Control Supervisor.

Counter-samples of all raw materials shall be taken in sufficient quantities for two complete repeat analyses. The counter-samples shall be kept for up to a year after the expiry date of the last finished product in which the raw material lot is used. The counter-samples shall be stored at suitable temperatures.

The analysis methods shall be suitable for the analytical test required. If methods other than those supplied by international bodies are used, analytical validation data shall be available to confirm the specificity, precision, accuracy and linearity of the method in the working range, limit of detection (LOD) and limit of quantification (LOQ).

Any external laboratories used to support the testing activity shall be accredited for the analytical test required. The accreditation shall be recognised by an official national or international body. Otherwise it will be necessary to have data validating the analysis method in order to confirm requisites regarding specificity, precision, accuracy, linearity in the working range, limit of detection (LOD) and limit of quantification (LOQ).

Reagents and solutions for the analytical tests and reference substances shall be stored in suitable conditions and be clearly labelled. The name, potency, expiry date, and where applicable, the date of preparation shall be clearly legible.

REPROCESSING

Reprocessing may be carried out in the following circumstances:

- repetition of a process phase for producing semi-finished products or intermediates;
- repackaging phases;
- sorting activities of defective units.

Reprocessing is ruled out when:

- it involves the processing of materials that are non-compliant due to the maximum level of contaminants provided for by legislation being exceeded with other materials that are, instead, compliant, solely for the purpose of diluting the contaminant level;
- it involves adding components not declared on the label in order to improve the product's chemical-physical characteristics.

Reprocessing may be authorised only if, following an adequate assessment of all the related risks, no potential effects are found in terms of the quality, efficacy and food safety of the finished product or deviations from release specifications.

The impact on the product's characteristics shall be carefully evaluated, if deemed necessary, with suitable risk analysis tools.

Reprocessing shall be:

- carried out in accordance with precise instructions, approved by the functions involved and documented in detail;
- agreed and authorised beforehand by the Customer if carried out by a third-party business.

Reprocessing shall be planned so as to guarantee:

- detailed reprocessing methods/instructions approved by the competent functions also based on deviations from the initial fabrication procedure;
- adequate hygienic conditions for handling the exposed product and/or provision of preventive measures so as to reduce to a minimum the risk of product contamination or mix-up of materials;
- suitable training of operators who have to carry out the reprocessing;
- suitable controls to check compliance with the finished product release specifications in accordance with specific sampling plans (additional quality controls to those normally specified, increase in frequency of IPCs);
- observance of the traceability criteria for the lot or fraction of a lot to be reprocessed;

- a detailed documented process. The records shall be kept in the archive for a suitable period compatible with the product's shelf-life;
- suitable shelf-life management when specified.

The portion of lot or product to be reprocessed shall be properly segregated and identified.

The reprocessed lot may be released only after establishing:

- that the product conforms to the specifications;
- the product conforms to the hygiene and health requirements;
- the reprocessing is managed correctly;
- the documentation collected is compliant.

TRANSPORT AND DISTRIBUTION

The basic requirements for food transport are laid down in (EC) Regulation 852/2004.

All operators should adopt suitable procedures so that the vehicles, loading bays and containers used during the entire transport phase for products leaving the production plant do not alter the quality and safe use of supplements. All available vehicles shall be appropriate for the type of goods transported, shall be maintained in a good state of repair, without any kind of damage so as to prevent the creation of hiding places for pests. Therefore, unsuitable vehicles (e.g. under repair or not properly sanitised) should be kept in a separate, properly demarcated area.

Before each loading operation vehicle conditions must be checked (e.g.: physical damage, presence of "fragile materials", abnormal smells, significant build-up of dust, presence of condensation, pests, mould) and the necessary measures taken.

If a damaged product is loaded onto a transport vehicle, it should be kept separate and properly segregated from the sound product; in addition, it should be handled so as not to expose the other products present on the vehicle to any contamination or infestation.

It is necessary to set up effective procedures that can document that the product is sound during transport. These shall include:

- any restrictions on the use of mixed loads;
- requirements for product safety during transport, particularly when the vehicle is stationary or unsupervised;
- clear instructions to be followed in the event of damage, accident or fault in the refrigeration systems. The safety precautions should include means of dissuasion and prevention in order to prevent any possible tampering with goods found during the storage and distribution phases.

If storage or transport activities are outsourced to third parties, the premises, vehicles and their internal conditions should be checked periodically in order to eliminate any risks of contamination.

Procedures should be implemented to prevent the transport of raw materials, intermediates or finished products in the presence of hazardous products. All these requirements shall be clearly defined in the contract and properly verified.

If a temperature control is required, the transport vehicle shall be able to maintain product temperature within the specified limits, in minimum and maximum load conditions. The instruments able to record temperature data shall be suitable; such instruments may be used to confirm the time/temperature

conditions, or to monitor and record at a pre-set frequency that plant is working properly. All documentation relating to measurements and calibrations shall be preserved properly.

To reduce the occurrence of physical changes to products requiring particular attention (e.g.: risk of soft capsules melting), suitable instructions shall be given in order to reduce any large temperature fluctuations during the transport and delivery phases.

Therefore, vehicles used to transport products where temperature monitoring is found to be necessary should use refrigeration systems designed and developed to ensure that the temperature is maintained during the journey within the range set by the producer. The refrigeration systems fitted to these vehicles shall be able to provide the necessary refrigeration power to cancel out the thermal flows entering from outside.

The transport operative or the responsible person has the task of carrying out regular checks on the correct temperature of the product at the time of loading (for example using data-loggers) and is responsible for arranging the goods properly inside the vehicle, in order to ensure that cold air circulates correctly and avoid unnecessary door opening. In addition, the transport operatives are responsible for ordinary and extraordinary maintenance both of the vehicle's isothermal van and the refrigeration system.

The temperature regulation and recording systems fitted to the vehicle shall provide detailed information on the temperature pattern and plant performance throughout the journey. This record, kept on electronic or computer media, constitutes proof of the conditions in which the product has been transported.

Forklifts and other trucks used inside the storage areas shall normally be battery-operated or equipped to prevent fume or fuel contaminations.

QUALIFICATION AND MONITORING OF SUPPLIERS

Each operator should adopt a procedure for the qualification and periodic monitoring of all suppliers of raw materials, packaging materials, finished products [contractors] or other critical services that have a direct influence on the quality of the product for the consumer.

The supplier qualification and monitoring procedure shall define the general criteria, the responsibilities and working practices adopted by the operator to manage and control all the phases of the supplier assessment process and maintain a list of qualified suppliers for product or service quality purposes.

Supplier assessment

The aim of the assessment process, generally entrusted to a special team, is to determine the supplier's manufacturing capabilities, checking that the quality requirements defined by the operator are met.

The *assessment criteria* are set by the operator based on a knowledge of the supplier and may include:

- assessment questionnaires (new suppliers) or analyses of historic data;
- sampling assessment;
- direct inspection checks at the supplier's premises;
- third party assessments.

Based on the level of knowledge of the supplier and with reference to product quality, the activity carried out (e.g.: production vs distribution) and the product or service required, the team assesses a set of parameters, including:

- business structure and technical-production capabilities;
- compliance of the product/service supplied with the required standards;
- system and product certifications.

The *frequency of periodic checks* is decided by the operator in line with the criticality index assigned based on given risk factors (percentages of non-conformities on the lots consigned, score achieved by the answers to the questionnaire, presence of certifications, etc.).

Documentation

It is opportune to keep a suppliers' database containing all production and administrative information, quality status and all data relating to the respective assessments.

All documentation should be kept for at least three years from the last update.

In addition, regarding the management of service suppliers, the business shall provide for documented procedures for the following:

- pest control,
- cleaning,
- equipment assistance and maintenance,
- transport and distribution,
- storage of ingredients or finished products,
- laboratory tests,
- waste management.

Management of Outsourcing processes

The business must be able to prove that, in the case of outsourced processes or parts of processes, such aspects are shared with the brand proprietor and, if necessary, authorisation must be provided.
The business shall also ensure that the enterprises to which a process is outsourced are monitored, through the favourable outcome of documented checks at the supplier's premises, in order to assess its food safety, traceability and compliance with the HACCP and GMP protocol. Such inspections shall be carried out by experienced inspectors with proven expertise in such matters.
All the outsourced operations shall be carried out in accordance with the terms signed in the contract between the parties and their complete traceability guaranteed.

Marketing of products produced by third parties

When a food business operator (FBO) markets products produced by third parties, implementation of a suppliers' approval and monitoring process shall be assured.
This process shall also contain clear assessment criteria such as: audits, analysis certificates, supplier's reliability and complaints.
In the case of private brands, a supplier's approval system shall exist in accordance with the requirements laid down by the proprietor of the brand for sub-suppliers of finished products.

PRODUCT COMPLAINTS, WITHDRAWAL AND RECALL

This section of the guidelines applies to all operators in the food sector who are responsible for receiving complaints about quality problems and/or reports of events harmful for health related to food supplements.

Legal requirements

(EC) Regulation 178/2002, which sets up a rapid alert system for notifying a direct or indirect risk for human health, due to the use of foodstuffs or animal feed, provides for procedures not only for the traceability and withdrawal of food not considered safe but also for its recall, if the food not compliant with safety requirements, as defined in article 14 of (EC) Regulation 178/2002, has already been released for consumption.

European food safety legislation hence identifies the FBO as being responsible for the safety of products placed on the market and states that each member State must inform the Commission, through the rapid alert system, of any measure that has been adopted to limit the risks for the consumer, including any proposals to withdraw or recall the product implemented by the FBO, in accordance with the requirements of articles 18, 19 and 20 of (EC) Regulation 178/2002.

According to the requirements of this regulation, if a food business considers, or has reason to believe, that a food supplement that it has imported, produced, manufactured or distributed does not comply with the food safety requirements, it shall immediately start procedures to withdraw the product in question from the market. The business must also inform the competent authorities of the country(ies) in which the product is marketed and collaborate with the authorities regarding the actions adopted to prevent or reduce the risks related to the product.

The regulatory framework also requires the competent authorities to be informed if a business considers, or has reason to believe, that a product placed on the market may be prejudicial to health.

Receiving complaints

As prescribed by legislation, the FBOs shall adopt suitable procedures for receiving, assessing and handling all consumer complaints received by the business. These should be able to handle:

- complaints regarding quality problems only, having no impact on health;
- complaints regarding adverse events;
- the periodic recording and review of complaints may be delegated to experienced trained personnel, but the general control and overview of complaints about adverse events should be maintained by the candidate named as responsible.

Handling complaints

Complaints about the quality of the food product

Complaints that have no impact on health and only concern problems with finished product quality (for example, flaws with labelling, packaging or weight, etc.) shall be addressed directly to the Quality Assurance department and may involve Regulatory Affairs.

Where possible, complaints about food product quality should be carefully examined by suitably qualified personnel, who have fully understood the significance of the complaint received and who may also know about similar or related complaints. Every complaint received should be logged and the reports should be the basis for subsequent actions. The contact form that the business should send to the party who has submitted the complaint (end consumer, intermediary, retailer, etc.) should at least indicate:

- information for identifying the complainant;
- useful contacts;
- data on the product/s involved (product brand name, lot code and any useful information);
- nature of the alleged defect.

This information will be useful for defining the product and the lot involved and checking the plausibility of the defect reported. If the complaint is justified, measures shall be adopted to eliminate or resolve the cause and prevent its recurrence.

Withdrawal or recall procedures

Based on the type and extent of a complaint about a food product (quality flaw/s or non-compliance with the declared standards) that has been verified and deemed to be plausible, the FBO is required è prepare, if necessary, procedures for withdrawing or recalling the product, which should be implemented quickly, at any time, in or outside working hours.

A responsible person should be named to start and coordinate all the recall and withdrawal activities and, if necessary, be the point of contact with the competent authority. A crisis procedure and a management team shall also be set up to involve the section responsible for quality control, regulatory affairs and logistics.

To enable the food products involved in the recall or withdrawal to be intercepted, the FBO should inform the intermediaries, retailers and any party involved in transporting the food products involved. To enable this to happen, the notice of withdrawal or recall should include the following information:

- name, format and adequate description of the product;

- identification of lots;
- nature of the defect;
- action required, indicating the degree of urgency;
- name and useful contact details.

Complaints about adverse events

For adverse events caused by the consumption of food products, it is necessary to have a phase for assessing the event reported and an appropriate action in response.

An event that isadverse to health is any event where it is suspected that use of a food product has caused a collateral effect in one or more consumers. This would include, but is not limited to events such as: urticaria, diarrhoea, skin eruptions, irritation, stomach upsets, headache, etc.

Cases of events adverse for human health may be catalogued as:

Level 1: no plausible link between adverse effect(s) reported and food product.

Level 2: the potential negative effects are known, but the link between adverse effect(s) reported and food product is not verified or is not verifiable.

Level 3: slight negative effects, when the person has reported slightly traumatic symptoms that have quickly resolved themselves. The effects may include skin irritations, pruritus, conjunctivitis, drowsiness, transitory coughing, headache, joint pain, agitation, anxiety or slight gastrointestinal symptoms such as self-limiting diarrhoea, stomach cramps or nausea.

Level 4: serious negative effect(s), when the person has presented with more pronounced symptoms, which are prolonged over time or of a more systemic nature than Level 3 symptoms. Requiring medical treatment or are the cause of hospitalisation or death.

When a report is received of an event adverse for human health, the FBO should contact as soon as possible the consumer/s involved using a standard questionnaire to allow an investigation into the adverse event and guarantee the complaint's authenticity. The response questionnaire should request an adequate level of information and should at least report:

- information for identifying the complainant;
- useful contacts;
- details of the product in question (name and lot code and any useful information);
- details of consumption/exposure to the food product;
- the nature of the alleged adverse event and timings of occurrence;
- known allergies and significant clinical data.

A report of an undesired effect could be considered to be verified on receipt if reported by healthcare professionals and doctors or through direct communication by a competent health authority.
A qualified person shall be responsible for carrying out and monitoring the complaint procedure for an event adverse for human health and for reviewing the reports of all complaints received by the FBO.
FBO personnel should be properly trained in the adverse complaint procedure, to ensure that all the complaints are sent to the person responsible or to their deputies in an effective and timely manner.
All adverse event complaints should be logged with as much detail as possible. The adverse event reports should be kept in a centralised system that should be easily accessible by the person responsible.

Risk assessment

Taking account of the information required to assess the extent of the case reported and ensure the safety of a food involved, the FBO should draw up a dossier to collect most of the information listed below:

I. Identification of the food product

1. Name of the food product;
2. The lot code, formula number and traceability system in place.

II. Product production method

1. Description of the manufacturing process;
2. Description of the packaging;
3. Declaration of conformity with the GMP applied;
4. Expiry date and method used to determine it.

III. Assessment of food supplement safety

1. Quantitative and qualitative composition of the product;
2. Physical/chemical and stability characteristics of the product;
3. Microbiological quality;
4. Impurities, traces, information about the packaging material;
5. Correct use and recommended daily dose;
6. Exposure to the end product/daily dose;
7. Exposure of each ingredient and, if applicable, the concentrations of substances to be monitored;
8. Toxicological profile of substances / Toxicological assessment;

9. Undesired effects and any known serious adverse events;
10. Conclusion of the assessment.

After collecting the information previously reported and concluding an appropriate assessment of the case, the actions to be taken differ based on the extent of the adverse effects reported:

Level 1 Event: no link between effect and food product.

1. Collect the complaint from the consumer or report from the healthcare professional.
2. Respond to the consumer or healthcare professional who has reported the case.

Level 2 Event: the potential negative effects are known, but the link between effect and food product is not verified/verifiable.

1. Collect the complaint from the consumer or report from the healthcare professional.
2. Define whether the product is really responsible for the adverse effects reported.
3. Respond to the consumer or healthcare professional who has reported the case.

Level 3 Event: Slight negative effects

1. Collect the complaint from the consumer or report from the healthcare professional.
2. Collect useful information for a correct assessment of the case and product involved.
3. Define whether the product is really responsible for the adverse effects reported.
4. Respond to the consumer or healthcare professional who has reported the case.
4. Inform the authorities if involved.
5. If necessary, establish a possible recall campaign for specific lots of the food product involved

Level 4 Event: serious negative effect

1. Collect the complaint from the consumer or report from the healthcare professional or competent authority.
2. Collect useful information for a correct assessment of the case and product involved.
3. Define how the product is responsible for the adverse effects reported.
6. Respond to the consumer or report by the healthcare professional.
7. Inform the authorities involved.
8. Set up a recall campaign for the food product involved.

Post recall/withdrawal actions

Procedures must be put in place to ensure the correct handling of the material or product withdrawn or recalled, which should be placed in quarantine, pending a decision on the handling or appropriate disposal.

The complaint records should be regularly analysed, summarised and re-examined for any potential trends or indications of a need to recall a product or any other specific procedure. This is particularly important as regards adverse event claims.

The procedures for receiving complaints, managing crises, recall and withdrawal should be regularly reviewed to check whether there is a need for revision in view of the current position, circumstances or person responsible.

DOCUMENTATION

Good documentation is an essential and integral part of GMPs and underpins an effective HACCP system. The main purposes of adequate documentation to support good manufacturing practice for a food supplement are:

- to define the materials, operations, activities, control measures and products;
- to record and communicate the necessary information before, during or after manufacture;
- to reduce the risk of error arising from verbal communication;
- to allow the investigation and research of defective products.

The documentation system shall be such as to allow the "history" of each production lot to be reconstructed, including use and disposal of raw materials, intermediates and loose or finished products thereby maintaining their traceability, as required by European legislation.

Type of Documents

a. Formulae for production and processing and packaging instructions

These indicate all the starting materials used and define all the processing and packaging operations.

b. Specifications

These describe in detail the requirements with which the products or materials used or obtained during manufacture shall comply. They serve as a basis for quality assessment.

c. Procedures

These provide guidance on carrying out certain operations, for example cleaning, clothing, environmental control, sampling, tests, equipment operation.

d. Records

These give the history of each product lot, including its distribution, as well as the other circumstances pertaining to the quality of the end product.

Classes of Documents

The following lists are not exhaustive but indicate the recommended documentation:

a. Specifications, instructions and procedures

- specifications of ingredients;
- specifications of packaging materials;
- copy of the order and/or purchase condition terms;

- master manufacturing instructions (including the standard recipes);
- intermediate specifications;
- bulk specifications;
- finished product specifications;
- quality control procedures and methods (including analytical and microbiological);
- standard procedure for product recall;
- the plant's operating instructions;
- cleaning instructions, cleaning plans and parasite control programmes;
- plant maintenance times;
- quality control programme.

b. Records and reports

- goods inwards data, test reports, approval and release for use of raw materials and packaging materials;
- record of tests and release of intermediates, bulk products and finished products;
- records of process control tests;
- graphs of recording instruments in progress;
- weight or volume control graphs;
- lot production record;
- product distribution authorisation records;
- production, distribution, analysis and other subcontracts;
- customer complaint documentation;
- quality control investigation reports;
- quality review reports and records;
- HACCP review report;
- training documentation;
- superseded documents.

c. Programmes

- production programmes;
- calibration programmes;
- validation/verification programmes;
- training programmes;
- quality audits.

Organisation of Documentation

Documentation should also include procedures for handling problems, authorisations, distribution and periodic revisions.

Sufficient training on completion of documents shall be provided to the competent personnel and the training's adequacy shall be regularly assessed.

Only authorised personnel may enter data and amend documentation. Any hand-written changes shall be made clearly and legibly, using indelible ink and be confirmed with the addition of the initials of the author of the change and/or signature.

The documents shall contain all necessary, but not superfluous, data. Any heading or section for entering items no longer in force shall be removed.

The documents shall be up to date. Any change shall be formally authorised and signed by the authorised responsible person. The obsolete document shall be substituted as soon as possible with the rectified document.

The documentation system shall include procedures for issue, authorisation, distribution, periodic control and revision.

An obsolete or superseded document shall be removed from active use and a copy, countersigned with the replacement, is to be kept for reference.

It may be useful to prepare a manual describing the general quality control system, the procedures followed, and the documents used. This shall be fully integrated with the HACCP documentation and made available to all competent personnel.

Electronic Documentation

If the documentation is stored electronically, sufficient backups shall be carried out so that the original data can be recovered in the event of changes, damage, deletion or destruction of the file. The system shall be protected against unauthorised access. Procedures illustrating release, revocation or change to the authorisation, as well as actions to be taken in the event of system error or fault, shall be drawn up.

Any computer used to control critical operations, such as state of quarantine/release, shall be set so as to allow only authorised personnel to access and control changes.

Conservation of documents

The period for conserving documents depends on their function. Consideration shall be given to all the legal requirements, including national requirements, and the supply of proof of due diligence evidence in the event of control by the Authorities.

As a general guide:

- the lot records shall be kept for a period of one year after the product's shelf-life;
- weights and measures of the control logs shall be kept for a minimum period of one year and one day.

Vice versa, documents containing redundant data should be removed through a continual monitoring system.

Finally, it would be desirable to use fireproof safes to store backup documents**.**

CHAPTER II

- *Botanicals* -

INTRODUCTION

"Botanicals" are ingredients produced from plant matrix, such as fruit, plants, spices, herbal infusions and others.

These ingredients can derive from whole plants or parts thereof. It is also possible to obtain functional substances, produced through different plant matrix processes such as extraction, squeezing, fractionation, distillation, concentration, drying and others.

Botanical-based food supplements are defined as all products regulated by Directive 2002/46/EC, adopted at national level through Legilsative Decree no. 169 of 21 May 2004, and consisting of plants or parts thereof, algae, fungi and lichens. Reference is made to the general part for the regulatory framework.

At European level there is no specific legislation for food supplements containing "botanicals"., so, all the regulations in place for food supplements apply to all the phases involving production, processing, packaging, distribution, storage, sale and administration.

The preparation of botanical-based food supplement labels follows Directive 2002/46 and EU Regulation 1169/2011 and Regulation 1924/2006 that sets out the rules for using nutritional and health indications (Claims) that may be proposed on food labels and/or with advertising, with the aim of protecting consumer health and making them more aware of choices through correct information.

The Italian regulatory framework provides for the possibility of claiming physiological effects for a part of the botanicals allowed in the production of food supplements. Pending the definition of botanical-related claims at european level, the possibility remains to continue to claim the indications on the physiological effects admitted to date and available on the Ministry of Health website.

The permitted botanicals are those of Annex I to the Decree of 10 August 2018 *"Disciplina dell'impiego negli integratori alimentari di sostanze e preparati vegetali*" as amended by Decreto dirigenziale 9 gennaio 2019.

The latter contains the list of eligible plants and related parts, accompanied by the provisions for use. The list is flanked by the reference indications for the physiological effects of the ministerial guidelines on the subject, which are not part of the Ministerial Decree of 10 August 2018 as amended in Annex 1 of the Decree of 9 January 2019.

The same Decree in Annex 2 contains the *"Linee guida sulla documentazione a supporto dell'impiego di sostanze e preparati vegetali (botanicals) negli integratori alimentari"*. The purpose of this document is to provide businesses operating in Italy with specific information on the required documentation, the assessments to be carried out and the checks to be organised so as to obtain an effective and safe product for the consumer.

SELECTION OF STARTING MATERIAL

Origin

Considering that botanicals are plants, algae, fungi and lichens that can either be used as ingredients as they are or by selecting a part thereof, or by producing a preparation from them; it is important to monitor the aspects that affect the quality of the raw materials.

The key aspects affecting the growth of botanical raw materials are multiple and certain differences in these factors create a different chemical profile, in other words a different concentration of physiologically active substances.

These factors are primarily the geographical cultivation zone, the type of soil and cultivation, the presence of water, the temperatures and the cultivation and harvesting season.

It is therefore important to subject the lots of botanical raw materials to appropriate tests in order to ensure the concentration of physiologically active substances required for the efficacy of the ingredient which will then be used in the food supplement. Obviously as this is a raw material subject to multiple external factors a certain degree of variability must be allowed.

Such checks should include identification and purity tests to check for the presence and concentration of physiologically active substances, other quality markers.

It is important to carry out assessments on some of the external factors such as the geographical zone of provenance, the type of harvest: wild or cultivated, the cultivation and harvest time.

To ensure that the raw material and its purity are properly identified it is essential that the suppliers of such products follow the principles of Good Agricultural Practice (GAP) to ensure all requirements are met, in addition to traceability.

Identification and characterisation

To correctly identify the plant, algae, fungus or lichen it is always advisable to use the scientific nomenclature, since common names may vary from one geographical region to another and in certain cases be attributed to different species.

For this purpose, reference can be made to the following databases, which can be consulted free of charge:

www.theplantlist.org

www.ars-grin.gov

www.algaebase.org

www.indexfungorum.org

www.lichens.ie

The information that serves to uniquely identify the starting material includes:

- scientific name: full systematic name, including: family, genus, species, sub-species, variety, name of the author who described the species
- any synonyms
- common name
- part used: root, rhizome, tuber, bulb, wood, leaves, flowering tops, flowers, fruits, seeds, young branches, bark, etc. The whole plant means the plant including the part above the ground and the part below the ground
- geographical origin: continent, nation, region
- growing and harvest conditions: wild or cultivated plant, cultivation practices adopted, time of harvest in relation both to the season and the plant's development stage

Confirmation of identity

The identity should be confirmed at least by:

- macroscopic examination
- microscopic examination
- chromatographic techniques, if necessary
- other specific tests

Certain pharmacopeia or other monographs sometimes describe the tests to be carried out to be able to proceed with the identification of a botanical raw material.

Other chemical-physical tests may be carried out (also found in some pharmacopeia) to help with the identification or in any event help verify the raw material's quality:

- presence of foreign matter
- presence of other plants
- drying loss
- total ash
- insoluble ash
- hydrosoluble substances

Purity

Spectrophotometric tests, gravimetric tests, tests in HPLC or other tests, designed to extract from the raw material the functional substance of interest for which the plant is used, may be carried out to check the purity of botanical raw materials.
Some pharmacopeia contain tests to be carried out to assess the functional substances of interest in quantitative terms.

Contaminations

Foreign bodies

Post-collection material shall be subject to visual or physical analyses to identify and remove any foreign bodies (stones, soil, insects or parts thereof, metal fragments from agricultural machinery etc.).

Cross-contaminations between plants or parts of the same plant

The regular conduct of plant identification tests (cfr. paragraph 3) should be able to identify any adulterations or cross-contaminations due to the co-existence of several plants in the same environment.
In addition, since some parts of the same plant are suitable for human consumption whilst others may contain undesirable substances (such as allergens), the presence of parts other than those permitted by the relevant regulations must also be identified.
When it is not possible to make effective selections, the material is to be rejected.
In fact, Annex I to the Decree of 10 August 2018 *"Disciplina dell'impiego negli integratori alimentari di sostanze e preparati vegetali"* include guidance on the part of the botanical raw material that may be used as an ingredient.
For a broader understanding of the undesirable substances present in certain plants or parts thereof, the *EFSA Compendium on botanicals*[1] represents a valuable tool for consultation.

Chemical contaminations

The main sources of chemical consultation are the surrounding environment, agricultural practices adopted and post-collection treatments.

[1]EFSA Compendium: https://www.efsa.europa.eu/it/data/compendium-botanicals

The most common contaminants include: heavy metals, mycotoxins, dioxins, polycyclic aromatic hydrocarbons, radioactivity and anti-parasitic residues.

Some of these are regulated by European food regulations through maximum limits on plants or parts thereof. Others, although not yet subject to specific rules, may still be cause for concern for food safety purposes. One example is the possibility of cross-contaminations between different plants, at field level, which could give rise to the presence of unwanted secondary metabolites even in species that do *not* naturally produce them (e.g.: pyrrolizidine alkaloids, tropane alkaloids, etc.).

It is therefore essential that the operator responsible for the starting material adopts all the measures required to destroy or reduce the risk to acceptable levels even when there are no relevant regulatory requirements.

When it is not possible to eliminate the source of contamination the ALARA principle applies, already provided for by EEC Regulation no. 315 of 1993.

Finally, it should be remembered that, under European food legislation, any product which has a level of contaminants that exceeds the level allowed by the law may not be marketed for food production nor may it be 'diluted' with lots having a lower level of contamination in order to obtain a compliant product.

The monitoring of chemical contaminants on the raw materials used for Botanicals is therefore necessary both for monitoring the actual quality of the lot in question, but also for purposes of product supplier qualification.

Microbiological contaminations

Contamination by pathogen microorganisms is a serious risk for human health primarily when the cultivation soils are treated with fertilisers based on animal by-products or irrigated with surface waters; the type of irrigation may also affect a crop's bacterial load.

Contaminations may also occur during collection, storage, transport, drying and subsequent processing phases.

Routine tests on microbiological quality relating to:

- total plate count
- *Escherichia coli*
- *Salmonella spp.*
- Enterobacteriaceae
- moulds and yeasts

should be planned with a frequency that may vary depending on the type of cultivation and the plant's growing conditions.

Treatments

All treatments adopted to destroy the microbial load shall be legally allowed under European and national legislation and in any event shall not represent a risk for the health of the consumer nor shall it alter the organoleptic characteristics and properties of the starting material.

INGREDIENTS AND PLANT PREPARATIONS

Classification

As defined in the introductory section of these guidelines, the ingredients and plant preparations include both dried herbs, macerated or in powder form, and preparations such as tinctures, juices, essential oils and extracts.

Concentrates and dried preparations

These are obtained by removing the water component of the previously crushed fresh material (the whole organism or parts thereof): water removal may be partial (concentrates) or total (dried).

Dried preparations

These are obtained starting with dried material through:

- crushing hard bodies such as wood, rhizome roots, high-grade bark or mashing of herbaceous parts, leaves, flowers, buds, bulbs, tubers and fruits; the final preparation is rather coarse and uneven;
- pulverisation: gives a powdery consistency preparation with uniform grain size that varies depending on the pulverisation and sieving method used (coarse, large, semi-fine, fine and very fine).

These preparations may be simple when they consist of just one plant; compound them they are the result of a blend of preparations from several plants.

Extracts

Tinctures and mother tinctures

These are liquid preparations generally obtained starting from dried (tinctures) or fresh material (mother tinctures) through the action of a solvent on a raw material of plant origin. Depending on the solvent used they are classified as: alcoholic, aqueous, etherate, winey.

Alcoholic tinctures are those that are so commonly used that the international pharmacopeia states that a tincture with no further specification indicates an alcoholic solution obtained by extraction. Tinctures may be categorised as simple or compound depending on whether they are prepared from one or more herbs.

Oleolites

Solutions of phyto-complexes of medicinal plants obtained through the solvent action of a suitable oil on a dried or fresh herb.

Essential oils

Essential oils are complex mixtures of various kinds of organic substances (alcohols, aldehydes, ketones, terpenes etc.): once extracted they present as oily, liquid and volatile substances with the same fragrance as the plant from which they originate. They may be obtained through distillation (hot extraction) or by simply squeezing (cold extraction) the fresh starting material belonging to a single type of plant. Distillation in a current of steam is the technique used to extract the essential oils from material that is not heat-sensitive; by contrast, cold squeezing is used to extract the essential oils containing heat-sensitive components.

Juices

These are obtained mechanically by pressing the fresh starting material, previously crushed and treated with enzymes. The result is a far more complex preparation than the extract but is less concentrated.

Plant extracts

Strictly speaking, these extracts are preparations that are liquid (fluid extracts), solid (dried extracts) or of an intermediate consistency (soft extracts) obtained starting with plant raw materials that are generally dried.

Extracts may be subdivided based on the solvent, a few examples follow:

- aqueous extracts: when just water is used
- hydroalcoholic extracts: extracts with appropriate alcohol proof solvent
- alcoholic extracts: when 95° alcohol is used

The extraction process may isolate, concentrate or remove given components from the starting material.

The factors affecting the efficacy of the extraction process are:

- grain size of the herb/ideal harvesting time (“*tempo balsamico*”)
- extraction solvent

- herb/solvent ratio
- agitation
- herb/solvent contact time
- extraction temperature

The product obtained is the *native extract*, to which excipients and additives for a technological purpose may be added; in this case one speaks of a *commercial extract*.

Plant mass ratio: extract, extraction solvents and markers

The *plant mass ratio: extract o* is the weight ratio of the mass of the starting material entering the extraction process to the mass of the extract obtained. In general principle, this may refer either to the native extract or the commercial extract but must be clearly indicated in the technical documents relating to the extract.
For dried extracts, due to the starting material's natural variability, the plant *mass ratio: extract* varies within an experimentally established range peculiar to the combination of the starting material/solvent used (e.g.: 3-5 : 1).

The choice of *extraction solvents* is a critical aspect of the extraction process, since it can determine the selective concentration of physiologically active constituents but also of unwanted or contaminating substances.
In any case the solvent or combination of solvents used must be permitted by food legislation on extraction solvents; residues found in the extract must comply with any maximum residue limits.

Markers

A *marker* is a characteristic, chemically defined, component, found in a plant preparation. Markers may be classified into two categories:

- active markers, namely components or group of components for which a physiological effect is recognised;
- analytical markers, namely components or group of components characteristic of the original plant, algae, fungus or lichen for which analytical measurement methods exist; these *markers* are used to confirm the identity of the plant preparation.

It should be remembered that the ideal *marker* is a substance for which an analytical and validated analysis method exists that is not subject to interference by other components present in the starting material or originating in the production process.
Both active and analytical *markers* may be used for quality control purposes.

Description of extracts

Standardised extract

The standardisation of extracts is carried out by adjusting, with tolerance limits, the titre/concentration of physiologically active components by adding excipients (e.g.: maltodextrin) or mixing different lots from the same extract. Any excipients with a supporting function or additives may be used but only in the quantities strictly necessary and/or allowed by legislation on food additives.

Quantified extract

Quantified extracts undergo adjustments to obtain a defined range of constituents that contribute to the physiological activity characterising the extract itself. The adjustments are carried out only by mixing batches with a different concentration of characterising substances to achieve the desired level. Any excipients with a support function and additives may be used but only in the quantities strictly necessary and/or allowed by legislation on food additives.

Other extracts

Extracts the physiologically active constituents of which have not been clearly identified may be defined through their production process and appropriate specifications.
For these extracts it is particularly important for the plant mass: extract ratio chosen to reflect as far as possible the composition relating to the constituents originally found in the part of the plant, algae, fungus or lichen used.

Safety and quality criteria

European food legislation does not, to date, provide for the application of maximum levels of specific chemical or microbiological contaminants for ingredients/plant preparations.
However, different chemical contaminants as well as residues of antiparasitics are regulated at the level of plant, algae, fungus or lichen or parts thereof. It is therefore fundamental for the ingredient/plant preparation producers to verify that the starting material complies with the applicable

regulations through monitoring plans for the starting material and suitable qualification procedures for its own suppliers. At the same time, it shall be able to justify downstream any deviations from the maximum antiparasitic and contaminant limits established for the starting material taking account of the concentration/dilution factors determined by the transformation process applied. Even if limits are established for the end product (e.g.: heavy metals, polycyclic aromatic hydrocarbons in food supplements), but the source of contamination is the plant, algae, fungus or lichen, the ingredient/preparation producer shall still demonstrate that it has adopted all the necessary measures to contain the risk and give proof thereof to the user downstream. This approach should also extend to any unwanted substances characteristic of the plant, algae, fungus or lichen and to the measures necessary to avoid their presence in the ingredient/preparation.

The European pharmacopeia is a useful reference for a botanical's microbiological specifications. The ingredient/plant preparation producer is in any event responsible for carrying out a study on its own production process to identify and contain any phases that may affect the microbiological quality of the ingredient/finished product and that takes into account the modes of preparation and consumption. The assessment shall be based on a detailed analysis of the hazards.

European legislation requires all food supplements to contain an indication of the product's sell-by date.

The food supplement producer is responsible for defining a minimum product durability date, based on product stability studies in the final packaging stage. This indication may derive either from stability studies carried out on the specific food supplement or on data obtained from previous studies or studies carried out on similar products.

In addition, a preliminary study of the potential presence of hazardous or unwanted substances deriving from plant origin ingredients must be carried out as early as during the botanical food supplement's development stage: so, assessments are required, supported by information already contained in the literature and from traditional usage for that specific botanical raw material. The botanicals Compendium database is also an important aid for identifying possible hazards linked to the use of a specific raw material.

Commercial preparations: documentary aspects

In accordance with European legislation, each food business operator shall have all the information necessary to carry out its respective activity in full compliance with current regulations. It is important for the user of the botanical preparation or producer of the food supplement based on botanical preparations to obtain from its own suppliers not only the proper guarantees of conformity, safety and quality for the preparations supplied but also all the details of their composition. This is necessary both in order to label the finished product correctly (list of ingredients, quantity of substances with a physiological effect) and to assess, as far as possible, the legitimate use of the preparation based on traditional use as well as to evaluate, where necessary, the actual equivalence between preparations of alternative suppliers.

In particular, and taking account of the critical aspects illustrated in the previous chapter, the information obtained from the supplier shall, for the botanical raw materials and preparations, start with:

- botanical name of the plant (genus, species, any variety, author);
- geographical origin of the plant, growing conditions (wild or cultivated), collection period;
- part of the plant used;
- title of the physiologically active marker and/or other analytical markers;
- chemical-physical tests (also contained in certain pharmacopoeia) which may help to identify or in any event help with verifying the quality of the raw material;
- where possible, presence of any substances/secondary metabolites that are of concern;
- microbiological specifications and information on any methods used to destroy the microbial load;
- conformity of starting material with regulations applicable to antiparasitics and contaminants and description of the measures adopted to control the risks for the preparation, with related efficacy;
- description of post-collection processes;
- where pertinent, compliance with radioactivity regulations;
- confirmation of compliance with good agricultural practices (GAP) and harvesting practices relating to the starting material;
- any presence of allergens;
- any presence of genetically modified organisms (GMOs);

- description of the preparation: powdered drug, standardised extract, quantified extract, extract. If the preparation contains additives that are not permitted in the nutrients pursuant to Annexe III Part 5 of (EC) Regulation 1333/2008, the description shall include the additive in question (preparation 'X' + additive).

In addition, for the *extracts*:

- ratio of botanical mass (dry matter): extract mass. The ratio may refer either to the native extract or the commercial extract but shall be indicated unambiguously
- active or analytical markers and related quantification methods
- details of composition, including the quantities of: native extract, excipients relating to their function (support *vs* adjustments), additives
- microbiological quality of the extract
- specifications relating to any contaminants and antiparasitics present
- description of the extraction process and solvents used. This information is fundamental for ruling out the extract's categorisation as a novel food. In fact, it should be remembered that the traditional use is first and foremost a safety test; therefore, any production process that deviates significantly in terms of techniques, solvents used, etc. from that traditionally used for that plant preparation, could be sufficient to qualify the product as an unauthorised novel food and, as a result, potentially not safe for human consumption
- conformity of solvents with current legislation and related residues and other applicable regulations

It should be highlighted that any extract where the physiologically active component has been added in a pure form (whether by synthesis or of natural origin) cannot be classified as an extract but as a mixture of extract and active component.

It should also be remembered that, in accordance with Italian Ministry of Health provisions, a single substance with a high level of purity, even if obtained from a botanical source, cannot be described as an "extract" titrated in that substance.

CHAPTER III

- Probiotics and prebiotics -

INTRODUCTION AND REGULATORY ASPECTS

Since 2002 with community directive 2002/46/EC on food supplements, products based solely on "*probiotics*" with no associated nutritional components have been legally allowed as food supplements.

At national level the "*physiological*" effect of promoting intestinal flora balance has always been considered useful for health and linked to the ability of a particular probiotic strain to colonise at intestinal level thanks to the contribution of a sufficient number of live cells with the quantities of consumption indicated.

Having acknowledged the opinion of EFSA which, in the evaluation of claims to be authorised pursuant to (EC) Regulation 1924/2006, has rejected all the claims presented because they do not demonstrate a cause-effect correlation, on the regulatory level the Italian Ministry's approach is based on recognising the "efficacy" and traditional use of probiotics rather than an indication about health, to be authorised in accordance with article 13.5 of (EC) Regulation 1924/2006.

The term "probiotic" was introduced for the first time in 1965 by Lilly and Stillwell, as opposed to antibiotics. Today the internationally accepted definition of the term "**probiotic**" is that provided in 2001 by a group of experts from the FAO and WHO: *"Live microorganisms which when administered in adequate amounts confer a health benefit on the host"*. Referring to the interpretation of the two international organisations, the Health Ministry, in Italy, has defined probiotics as *"Live and viable microorganisms which, when ingested in sufficient quantities, are proven to function in a manner beneficial for the organism"*.

Foods/supplements with probiotics mean foods that contain, in a sufficiently high number, live and viable probiotic microorganisms, able to reach the intestine, grow and exert a balancing action on the intestinal microflora through direct colonisation. These foods are hence able to promote and improve

the organism's physiological balance functions through a number of effects additional to the normal nutritional activities.

Foods/supplements with prebiotics refer to those foods that contain an adequate quantity of prebiotic molecules, i.e. non-digestible substances of food origin that are able to promote the development of certain microorganisms that are useful for humans.

Foods/symbiotic supplements contain both probiotic microorganisms and prebiotic substances.

The legislation for these products is regulated by the Italian Ministry of Health's GUIDELINES ON PROBIOTICS AND PREBIOTICS (last revision March 2018) that define all the requirements that this type of product must meet.

In fact, only products that comply with these guidelines in terms of their probiotic or prebiotic content, able to promote bacterial flora balance, may indicate this effect on the label and use terms that imply that it is "probiotic" and "prebiotic".

TAXONOMIC CHARACTERISATION

The taxonomic classification of a microorganism is a fundamental requirement to ensure its safe use since it allows it to be classified in a list of sufficiently characterised microorganisms, thanks to their long history of "safe use" in food products and/or supplements.

The list of species, generally bacterial, known and considered safe, has given rise to the list of QPS microorganisms (Qualified Presumption of Safety), thus obtaining QPS status; this "recognition" is useful during the scientific evaluation phase, above all when new probiotic microorganisms have to be placed on the market.

This list, also adopted by EFSA (European Food Safety Agency), is constantly updated by a group of scientific experts.

Identification at strain level is necessary, not merely for safety reasons but above all to assess probiotic efficacy. In fact, numerous evidence indicates that different strains of the same species may also have very different effects on the host. The different ways in which the various strains act is thus consolidated by the scientific literature and reported in the FAO/WHO documents: "*data obtained with one specific probiotic food cannot be extrapolated to other foods containing that particular probiotic strain or to other probiotic microorganisms"*, and also in the AFSSA document (*Agencie Française de sécurité Sanitaire des Aliments*): *"The quantity of probiotics passing live through the gut depends on the strain, the dose ingested, factors related to the host and the vector food*".

In the light of the above, the importance of taxonomic classification, whereby, in practice, the microorganism has to be classified both at species and at strain level, is very clear.

For a long time, phenotypic taxonomy was the basis for species classification, but this has always left uncertainty and therefore difficulty in interpretation, particularly regarding characterisation of the various biotypes (strains).

A major step forward was taken with the advent of molecular biology techniques, particularly those developed for the study of bacterial DNA.

Today, the integration of phenotypic and genotypic characterisation means that good operating compliance can be achieved, and this must be considered a fundamental requirement for marketing probiotic microorganisms to be added to food or food supplements.

Phenotypic identification

Phenotypic identification is, sometimes, considered to be "obsolete" but often, if used with a good operating scheme, it allows a valid base to be built and integration with information that may be obtained from genetic analyses.

Phenotypic investigations can provide information at species level only and are based on determining:

- the carbohydrate fermentation profile;
- the enzyme activity profile;
- the nature of the lactic acid isomers produced.

Genotypic identification

The evaluation with genetic investigations has the huge advantage of establishing the microorganism, with good precision, up to strain level. The genetic techniques are based on the ability to study all or parts of the bacterial DNA. There are many techniques that, over the years, have been refined for this purpose but, to date, the most accredited ones are those for species-level recognition that are based on the sequencing of DNA that codes for 16S ribosomal RNA (rDNA) or the complementary pairing of two DNA filaments (hybridisation).

On the other hand, the techniques for identifying the bacterial load may be so different that even the two control Bodies, the Italian Ministry of Health and the EFSA, suggest different approaches. For the Italian Ministry of Health, the strain may be identified using PFGE (*Pulse Field Gel Electrophoresis*) that determines the study of the chromosome's macro-restriction profile through pulse field electrophoresis. The EFSA, as well as the PFGE, also accepts methods that are gradually being optimised by international bodies. Recently, the Italian Ministry of Health has updated the acknowledged methods, in accordance with those identified by EFSA.

Summarising the guidance of the Italian Ministry of Health and the EFSA, the taxonomic identification shall be carried out using the following techniques:

<u>for species-level identification</u>

- sequencing of DNA that codes for 16S rRNA;
- hybridisation of DNA-DNA nucleic acids.

<u>for strain-level identification</u>

- PFGE (Pulse Field Gel Electrophoresis)
- MLST (Typing of multilocus sequences)
- RAPD- PCR (Random Amplification of Polymorphic DNA)
- AFLP (Amplified Fragment Length Polymorphism)
- WGM (Whole-Genome Mapping)
- other

As an alternative the EFSA suggests other methods that allow strain-level recognition:

ARDRA (Amplified Ribosomal DNA Restriction Analysis)
- other

The results of the analyses will lead to identification of a species to which the strain belongs, and the taxonomic nomenclature shall be recognised by the International Union of Microbiological Societies (IUMS).

Strain depositary

It is recommended that all probiotic strains used in products or food supplements be deposited at International Culture Collection. The strains deposited allows any exchanges or mutations that might occur to be monitored and, thanks to the strain library, is a storage backup. For this reason, the depositary is considered to be a byword for safety and the Culture Collection having IDA status, namely International Depositary Authority status, are guarantors of the strain's uniqueness.

Depositing at a Culture Collection is a mandatory step also if one wishes to proceed with any patent for the strain or the activities related thereto.

The aim of identifying probiotic strains uniquely derives from scientific proof showing how different strains, belonging to the same species, can behave in very different ways, sometimes in a precisely opposite way.

This claim gives rise to the *strain-dependence* concept whereby the probiotic characteristics have to be demonstrated on each strain studied.

QUANTITY OF PROBIOTIC MICROORGANISMS

Definition and evaluation of probiotic effects

The Italian Ministry of Health, in Italy, has defined probiotics as *"Live and vital microorganisms which, when ingested in sufficient quantities, are proven to function in a manner beneficial for the organism"*.

In functional terms a large amount of experimental data suggest that probiotics may help improve different functions in a variety of districts, demonstrating how different strains, even those belonging to the same species, may act in different, sometimes opposite, ways.

Microorganisms that can be used in food or food supplements must meet the following requirements:

- be used "traditionally" to improve the intestinal *microbiota* and hence to have demonstrated benefits for the host;
- have evaluated safe use (also in the light of the 2001 and 2002 FAO/WHO documents and the QPS concept for the bacterial safety evaluation by EFSA) demonstrating that they are not carriers of acquired and/or transmissible antibiotic-resistances;
- are live and viable at intestinal level and in suitable quantities to allow colonisation of the intestinal mucous.

Quantity

Little is known about the optimal quantity of live and viable probiotic bacteria to be ingested since this is definitely also sensitive to the type of recipient, as well as being dependent on the type of benefit one wishes to add through its ingestion. This quantity, in relation to the bacterial strain used, the association with other strains, the food matrix chosen and the industrial form of the product, is not easy to determine in practice.

Certainly, the quantity of microorganisms must be the number of bacterial cells required to influence the composition of the recipient's *microbiota*, by colonising it.

In general, based on the scientific evidence available, the minimum quantity that is sufficient to achieve temporary colonisation of the intestine, by a probiotic strain, is equal to at least 1 billion live and viable cells (10^9 CFU/day), for at least one of the strains present in the product's daily dose. In

the absence of specific dose-response studies, this value is the result of a number of indications in the 2005 AFSSA document:

"*The dose of probiotics ingested is an important factor to obtain high concentrations in the various compartments of the gastrointestinal tract" .... "It is often said that probiotic concentrations must be greater than or equal to 10^6 CFU/mL in the small intestine (ileum) and 10^8 CFU/g in the colon, but the scientific basis for these statements is relatively weak."..... "The concentrations in the colon have been proposed because they correspond to less than 1/1000 of the autochthonous flora present (which it could be reasonably expected has more chance of being active than flora present at even lower levels)."*

The quantity of a billion (10^9 CFU/day) is not binding since lower quantities may be allowed only if a scientific rationale exists to support such a choice and hence only if there are specific scientific studies proving that it is suitable and effective for that strain at that does since the probiotic properties are **strain-dependent**. The efficacy has to be demonstrated also when mixes of strains are used since it is not said that the activity demonstrated for individual strains will have a synergic effect, when used in association; depending on the effect studied, the interaction between the strains used may be negative.

Since the majority of probiotic products are made up of several microorganisms, each with its own functional action, it is necessary to know the quantity of each of the strains making up the mix that will be suitably studied for the purpose.

Counting methods

Given that these are organic products with live microorganisms, it is permitted to have an overdose to guarantee, up to the end of the shelf life, the amount declared on the label when the product is stored under the recommended conditions. The quantity of viable cells present in the product must be shown on the label for each strain.

The analysis methods used to define the quantity of microbial cells may differ depending on the species that have to be quantified.

Starting from the presumption that each viable cell is able to form a colony (Colony Forming Unit), it is recommended that methods based on counting the colonies in agar medium be used to calculate the number of live microorganisms relative to the microbial species declared on the label, that is

classic microbiology methods based on the growth, on a plate, of adequate serial dilutions of the specimen to be tested. The choice of the method and growing conditions for the microbial count uses standardised methods and/or specifications for each kind of microorganism to be tested. Such methods, if implemented with particular strategies, may allow a differential count in the case of a mix of several strains belonging to different strains. The use of particular devices that exploit the physiological properties of a bacterial species, such as the capacity to grow at different temperatures, the capacity to metabolise particular substrata, the capacity to form morphologically distinguishable colonies or to grow in the presence of antimicrobial substances, may be crucial for selective and/or differential growth.

The microbiological methods used for the plate count must be suitably verified and validated; a result uncertainty of 0.5 log is allowed for these methods due to their microbiological nature.

In this regard the *Istituto Superiore di Sanità* (ISS), in 2008, issued a document (ISTISAN Report 08/36) which describes in detail the microbiological methods recommended for counting probiotic microorganisms.

Minimal adjustments or different methods are permitted if justified for the specific probiotic/product.

Safety of probiotic microorganisms

Ascertaining the safety of microbial species proposed as probiotics for human use has always been a mainstay for the Regulatory Authorities, especially after publication of clinical reports on occasional infections attributable to their use, affecting immuno-compromised patients most of all.

For a long time, the marketing of probiotics, in the form of dairy products or food supplements, was not subject to a formal safety assessment due a long tradition of problem-free use for consumer health. It is precisely for this reason that, in the USA, many microorganisms are categorised as GRAS (G*enerally Recognized As Safe*) by the authorities and can be marketed freely.

Clinical studies and after-market control on products containing probiotic microorganisms (*Lactobacillus* and *Bifidobacterium*) have not revealed any adverse effect in consumers or persons treated, despite the large quantity of products consumed each year in many industrialised countries. The increased consumption of probiotic microorganisms has opened up a discussion on the possibility to define proper criteria in order to verify the safety of microbial cultures for human and animal uses.

The European Food Safety Authority (EFSA), being aware of this question, has developed and introduced a new system for a pre-market evaluation of the safety of selected groups of microorganisms, avoiding the use of microorganisms that are "carriers" of antibiotic resistances.

The importance of a taxonomic classification up to strain level has already been illustrated; on these basis *strain-dependence* concept rises, a mechanism whereby each strain has different distinctive features and the probiotic properties have to be studied and demonstrated on each individual strain.

The use of a new microbial strain, even if it belongs to a strain that is already known and normally used, requires a new efficacy and safety assessment.

For safety verification purposes, it is essential to give the strain, being studied, the right taxonomic identification at species and strain level so that its antibiotic-resistance profile (antibacterial or antifungal depending on circumstances) can also be built.

The antibiotic-resistance profile has to be determined for each individual microbial strain used, so as to rule out the presence of acquired resistance and resistance that is merely potentially transmissible.

When a new strain belonging to a "safe" species is isolated, as defined by the EFSA documents for QPS status for certain bacterial groups, it is not necessary to carry out in-depth studies but merely to characterise the new strain by evaluating its antibiotic resistance profile as recommended by FEEDAP in the specific Guidelines contained in the EFSA Journal of 2012;10(6):2740.

Antibiotic resistance profile

The method used to create the antibiotic resistance profile is an official method, recognised at international level, and is described in full in the document ISO 10932:2010 or IDF 223:2010.

This method uses a number of specific antimicrobial substances:

- Ampicillin
- Vancomycin
- Gentamycin
- Kanamycin
- Streptomycin
- Erythromycin
- Clindamycin
- Tetracycline

- Chloramphenicol
- Tylosin

These antimicrobial substances are tested in a defined range of concentrations so as to define, after incubation, the minimal microbial concentration inhibiting the growth of that specific strain (MIC) compared to the "cut-off", i.e. the threshold set by EFSA experts for the different probiotic species.

In the light of the results obtained, a microorganism is considered to be sensitive to a specific antibiotic when its growth is inhibited at least at the cut-off concentration (antibiotic minimal inhibiting concentration defined for each type of microorganism) and subsequent concentrations or if there is no growth in each well or growth is limited to the antibiotic concentrations below the cut-off concentration.

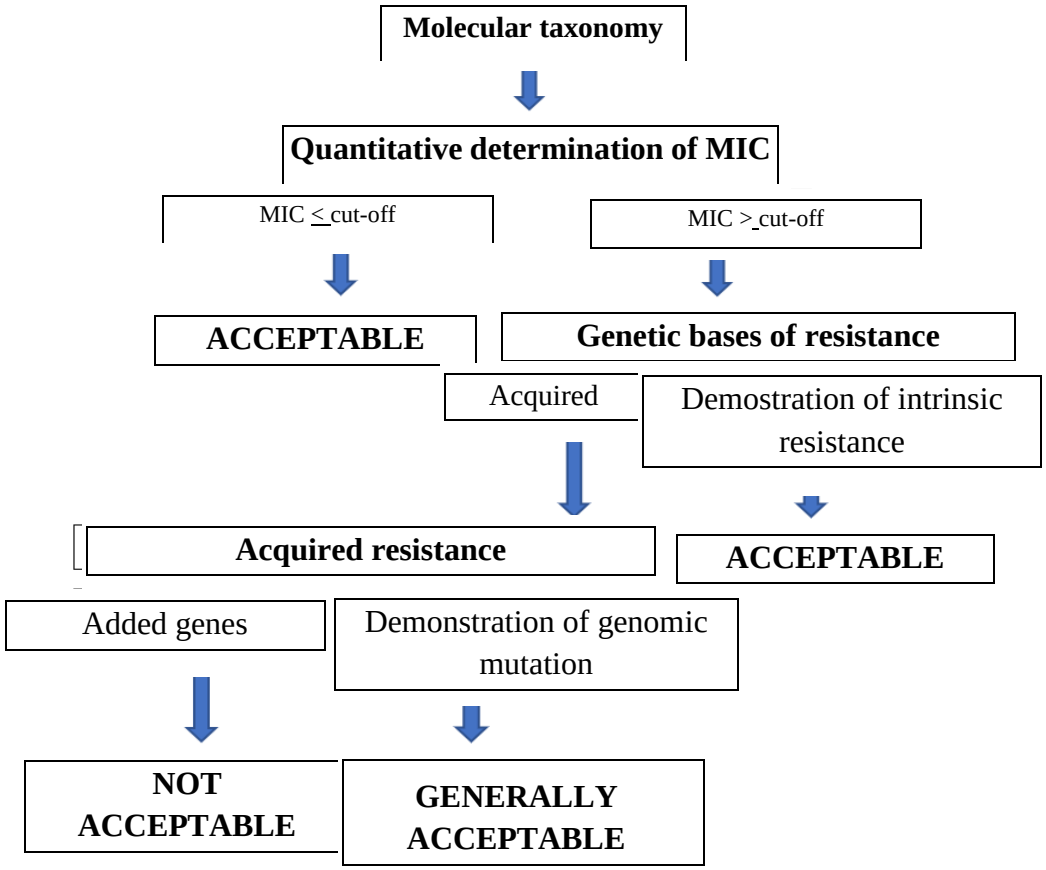
A microorganism is considered to be insensitive (resistant) to a specific antibiotic when its growth is not inhibited at the cut-off concentration, also involving growth at cut-off concentrations or higher concentrations.

Evaluation scheme

When a strain demonstrates greater insensitivity at the cut-off, identified by the FEEDAP, for one or more antimicrobial substances, further investigations are needed to establish the nature of the resistance. First and foremost, it is necessary to verify whether the resistance is intrinsic (i.e. it is typical of the species to which that strain belongs); in this case there is "natural resistance" and the strain is considered safe and hence acceptable.

When, instead, a strain, belonging to a species normally sensitive to a specific antimicrobial substance, is insensitive to the same concentration there is "acquired resistance". In this case it is necessary to investigate to establish the genetic bases of the resistance.

The approach adopted to evaluate the type of resistance is summarised in the following diagram:



Based on the diagram above the final considerations are:

- Any bacterial strain carrying an intrinsic resistance to antimicrobial(s) presents a minimal potential for horizontal dissemination that is acceptable and may hence be used.
- Any bacterial strain carrying an acquired resistance to antimicrobial(s) that is shown to be due to chromosomal mutation(s) presents a low potential for horizontal spread is “generally acceptable” and, in general principle, may be used.
- Any bacterial strain carrying an acquired resistance to antimicrobial(s) that is shown to be due to acquisitions of genetic determinants (e.g. plasmids) presents the greatest potential for horizontal spread that is “NOT acceptable” and must not be used.
- The strain should not be used in the absence of information about the genetic nature of a shown resistance.

PRODUCTION AND PACKAGING OF FOOD SUPPLEMENTS CONTAINING PROBIOTICS.

Introduction

More restrictive specifications have to be met for the production and packaging of food supplements containing probiotics than for the production of supplements containing vitamins and/or botanicals because probiotic strains are particularly sensitive to different external factors such as:

- Temperature.
- Ambient humidity.
- Water activity of the raw materials used and the semi-finished product produced.
- Initial load of the strain.

Characteristics of the raw materials used and of the semi-finished product

As probiotic semi-finished products are very thirsty for water, they have to meet more restrictive humidity limits than other product processes. Normally a calculation is made both of the humidity, which determines the quantity of water present in the product analysed, and water activity (Aw), which identifies the extracellular free water. The determination of the latter seems to be more significant and so it is very important to be able to ensure an Aw for the semi-finished product of less than 0.5%.

Keeping a low level of humidity during product preparation must be combined with an initial correct selection of the raw materials (other active components of the formula and excipients) for which an Aw of less than 0.2% is required.

When selecting the raw material to use:

- give preference to using excipients with a low Aw, where possible already dried by the supplier;
- if raw materials that meet the humidity specifications required are not available, evaluate the impact of drying procedures before mixing with the other components of the formula.

In capsule production, it would be advisable to consider the use of shells with a low LOD.

Regarding storage methods, raw materials and semi-finished products that have to be kept in a fridge should be conditioned at ambient temperature before they are used, for at least 12 hours, to prevent condensation forming when the packets are opened.

If small quantities of a freeze-dried probiotic are to be added to the mixture, the probiotic may be used as soon as it is removed from the fridge with no need for conditioning.

Overdosage of probiotic strains

In order to guarantee the strain load declared on the label to the end of the validity period, with an uncertainty up to 0.5 log, it is necessary to provide an overdose of the probiotic strains, the amount of which may depend on:

- the type of strain used, as a guide from 2 to10 times the quantity declared on the label;
- the type of product: in the production of tablets containing probiotics, taking account, right back in the development phase, of the fact that the compression phase could destroy at least one logarithm.

Adjustments to the amount of the overdose may be evaluated based on the results of stability studies.

Production

Before starting and during the production process it is necessary to ensure that the premises provided maintain the following ambient conditions:

- temperature between 20°C and 25°C
- relative humidity between 18% and 22%.

The premises provided for the preparation and primary packaging of products containing probiotics must therefore be fitted with:

- systems for controlling humidity;
- systems for controlling temperature;
- absolute filters for air treatment.

It is also important to pay the utmost attention to not using equipment that is not perfectly dry: drying equipment through the blowing of compressed air.

Primary packaging

It would be necessary to use more protective materials against heat and humidity to package products containing probiotics: preferring the use of primary packaging materials (blisters and wrap for sachets) that reduce the transfer of humidity.

Transport and storage methods

The initial transport of the strain, from the establishment where the standardised mixture is prepared to the finished product production establishment should be carried out on a controlled temperature vehicle. These raw materials must be in stored in a refrigerated unit (2-8°C).

The finished product, ready for distribution, may be kept:

- in an ambient with temperature ≤ 25°C (general case);
- in an ambient with temperature between 2-8°C (if the pack states that the product is to be kept in a fridge).

As a result, the same aforementioned conditions should be maintained during transport up to the sales environment and kept as such until used by the user.

Cleaning and sanitisation of premises and equipment

At the end of the preparation and primary packaging process for a semi-finished product containing probiotics the premises and equipment are cleaned using the same treatments applied to the other processes (important disinfectant rota to prevent resistance phenomena and the use of a different kind of disinfectants to destroy a wide spectrum of microorganisms).

It is important to pay the utmost attention to not using equipment that is not perfectly dry: drying equipment through the blowing of compressed air.

STABILITY STUDIES FOR PROBIOTIC PRODUCTS

The stability study should be conducted under the same temperature conditions indicated on the finished product label.
In the case of a new product, performance of a preliminary stability study enables the stability of the strain in the excipient base used and the compatibility with the other active constituents present in the formula to be identified. In the case of positive results, it will be possible to confirm the overdose proposed during the formulation stage, whilst if the load decays, it will be necessary to propose an increase in the overdose proportional to the decline.

To carry out the preliminary stability study correctly, a product sample is packed in the primary packaging proposed for marketing and stored for the times and in the conditions specified for the finished product.
In general, the thermo-hygrometric conditions under which the samples are stored during the preliminary stability phase are:

- 25°C ± 2°C – 60% ± 5% RH (general case);
- 5°C ± 3°C: this condition (if the pack indicates that the product is to be kept in the fridge).

Product storage at temperatures above 25°C (35°C/40°C, conditions used for the stability study of food supplements in general) is not considered to be significant, since fast declines of strain load are observed at such temperatures.

The commonly controlled parameters are:

- determination of the count: the ministerial guidelines indicate that the quantity of live cells must be guaranteed until the end of the product's validity with an uncertainty of 0.5 log. If the determination of the count shows a decline of more than two logarithmic orders of magnitude over the original value, the controls may be halted before the deadline planned by the stability protocol and the product will have to be reformulated;
- *Water Activity*: it is important to be able to guarantee a product Aw of less than 0.5; higher AW values are generally considered to be critical for the stability of the probiotic product.
- In general controls points at 1, 3, 6, 12, 18 and 24 months are considered.

Ongoing stability

The performance of an ongoing stability study on samples taken from the first manufacturing lots and kept in the conservation conditions envisaged for the finished product allows the product to be monitored, confirming or extending the shelf-life planned initially.

In general, the same conservation conditions indicated on the container for a period that is the same as or longer than the product's validity are considered when executing the ongoing stability study.

The control points and parameters observed are the same as those envisaged during the preliminary stability study.

GLOSSARY

ALARA: As Low As Reasonably Achievable

EC: European Community

EEC: European Economic Community

EFSA: European Food Safety Authority

FAO: Food and Agriculture Organization

FBO: Food Business Operator

GAP: Good Agricultural Practices

GMP: Good Manufacturing Practices

GRAS: Generally Recognized As Safe – United States standard whereby each substance that is intentionally added to a food product is considered to be a food additive subject to review and approval by the FDA, unless the substance is generally recognised, amongst qualified experts, as being adequately demonstrated as safe in the conditions of use specified or unless the use of the substance is otherwise provided for by the definition of a food additive.

HACCP: Hazard Analysis and Critical Control Points – is a set of procedures dedicated to preventing possible food contaminations by establishing analyses of the hazards and critical control points.

HPLC: High Performance Liquid Chromatography

LOD: Limit of Detection

LOQ: Limit of Quantification

GMO: Genetically Modified Organisms

WHO: World Health Organisation

QPS: Qualified Presumption of Safety

Quality Control Supervisor: Person responsible for quality assurance

RI: Reference Intake

Shelf-life: time period in which a food may be kept in specific conservation conditions to maintain its excellent quality and safety.

MCT: Minimum Durability

R.H.: Relative Humidity

DRV: Dietary Reference Values

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