



THE QUALITY AND SAFETY SYSTEM
FOR SPECIALTY FEED INGREDIENTS

PROCESS DOCUMENT PD-01 BIOPROCESS

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1. Introduction

The FAMI-QS Process Documents are auditable documents established for each process described in Chapter 2 of the FAMI-QS Code of Practice. Such documents include the requirements for the evaluation of the feed safety hazards associated with the Operator's processes with the view of controlling their occurrence.

The Process Documents are required to be used by Operators and Certification Bodies to assure that they operate their programmes in a consistent and equivalent manner.

The FAMI-QS Certified Feed Business Operators shall consider the applicable regulatory requirements of the country where their facility is located and the country where the products are intended to be placed. Bioprocess products must be traceable back to the microorganism/strain and deposition number where this is a regulatory requirement. This applies to producers and traders.

2. Definitions

Acceptable level: A level of hazard in a feed at or below which the feed is considered to be safe according to its intended use. (*Codex Alimentarius and adapted*)

Adequate: The terminologies “adequate”, “where appropriate”, “where necessary”, or “sufficient” mean that it is up to the Operator in first instance to decide whether a requirement is necessary, appropriate, adequate or sufficient to achieve the objectives stated in this document. In determining whether a requirement is adequate, appropriate, necessary, or sufficient, account should be taken to the nature of the feed and of its intended use. (*adapted from EC Guidance Document 2005 on Regulation 852/2004/EC and modified*)

Antimicrobial Resistance (AMR): refers to micro-organisms – bacteria, fungi, viruses, and parasites – that have acquired resistance to antimicrobial substances (*FAO Action Plan On Antimicrobial Resistance 2016-2020*) **And/or:** The ability of a microorganism to multiply or persist in the presence of an increased level of an antimicrobial agent relative to the susceptible counterpart of the same species. (*CXG 77-2011 - Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance*)

Bacteria: microscopic, single-celled organisms that thrive in diverse environments.

Batch: Unit of production from a single site using uniform production parameters or a number of such units, when produced in continuous order and stored together. It consists of an identifiable quantity of feed which is determined to have common characteristics, such as origin, variety, type of packing, packer, consignor or labelling.

Bioprocess: A process that uses biological material or its components to obtain the desired product. Bioprocessing is mainly based on upstream processes to produce biological material (cell culture, fermentation) and downstream processes which include recovery, separation/purification of the desired material/intermediate products, and possible preservation steps such as drying/freeze drying and formulation.

Calibration: The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

Carrier: Substance used to dissolve, dilute, disperse or otherwise physically modify a specialty feed ingredient in order to facilitate its handling, application or use without altering its technological function and without exerting any technological effect on the feed itself.

Cleaning: The removal of soil, feed residues, dirt, grease or other objectionable matter. *(Codex Alimentarius and adapted)*

Check/control:

- when used as a noun: The state wherein correct procedures are being followed and any established criteria are being met.
- when used as a verb: To take all necessary actions to ensure and maintain compliance with established criteria and procedures. *(Codex Alimentarius)*

Contaminant: Any biological, chemical or physical agent, foreign matter or other substances not intentionally added into or onto a raw material, intermediate, and products covered by FAMI-QS scope during production, sampling, packaging or repackaging, storage or transport, that may compromise feed safety or suitability. *(Codex Alimentarius and adapted)*

Contamination: The introduction or occurrence of a contaminant in the feed or feed environment. *(Codex Alimentarius and adapted)*

Control Measure: Any action and activity that can be used to prevent or eliminate a feed/food safety hazard or reduce it to an acceptable level. *(Codex Alimentarius and adapted)*

Corrective Action: Any action taken when a deviation occurs in order to re-establish control, segregate and determine the disposition of the affected product if any and prevent or minimize reoccurrence of the deviation. *(Codex Alimentarius)*

Critical Control Point (CCP): A step at which a control measure or control measures, essential to control a significant hazard, is/are applied in a HACCP system. *(Codex Alimentarius and adapted)*

Critical Limit: A criterion, observable or measurable, relating to a control measure at a CCP which separates acceptability from unacceptability of the feed. *(Codex Alimentarius and adapted)*

Cross-contamination: Contamination of a material or product with another material or product, including contamination originating from the previous use of equipment. *(CAC/GL 81-2013 - Guidance for Governments on Prioritizing Hazards in Feed)*

Deviation: Failure to meet a critical limit or to follow a GMP procedure. *(Codex Alimentarius and adapted)*

DNA: Deoxyribonucleic acid, or DNA, is a biological macromolecule that carries hereditary information in many organisms. DNA is necessary for the production of proteins, the regulation, metabolism, and reproduction of the cell. Large compressed DNA molecules with associated proteins, called chromatin, are mostly present inside the nucleus.

Documented Information: Information required to be controlled and maintained by an Operator and the medium on which it is contained. *(ISO 9001:2015 and adapted)*

Feed: Any substance or product, including specialty feed ingredients, whether processed, partially processed or unprocessed, intended to be used for oral feeding to animals. *(Regulation 178/2002/EC and adapted in EU)*

Feed Hygiene: The measures and conditions necessary to control hazards and to ensure fitness for animal consumption of a specialty feed ingredient(s) covered by the FAMI-QS scope, taking into account its intended use. *(Regulation 183/2005/EC in EU)*

Feed Safety: High level of assurance that the feed (feedingstuff, feed material or products covered by the FAMI-QS scope) will neither cause adverse health effects to the farm animals when prepared or consumed according to the

intended use, nor to the final consumer. Throughout the document, the word ‘*Safety*’ is taken to have the same meaning as ‘*Feed Safety*’.

Feed Safety Hazard: Biological, chemical or physical agent in feed, with the potential to cause an adverse health effect in animals and/or humans. *(Codex Alimentarius and adapted)*

Flow Diagram: A systematic representation of the sequence of steps used in the production or manufacture of feed. *(Codex Alimentarius and adapted)*

Fungi (singular: fungus): A kingdom of usually multicellular eukaryotic organisms that are heterotrophs (cannot make their own food) and have important roles in nutrient cycling in an ecosystem.

Gene(s) of Concern: Gene known to contribute to the production of toxic metabolites and antimicrobials of clinical relevance, or to AMR. For products with viable cells, other virulence factors are also included in this definition. *(EFSA Guidance on the characterisation of microorganisms used as feed additives or as production organisms, June 2018)*

Genetically modified organism (GMO): is an organism in which one or more genes (called transgenes) have been introduced into its genetic material from another organism using recombinant DNA technology. *(FAO definition)*

Good Manufacturing Practices (GMP): Fundamental measures and conditions applied at any step within the feed chain to provide safe and suitable feed. *(Codex Alimentarius and adapted)* - Equivalent term: PRP (Pre-requisite Programme) See FAMI-QS Code § 7. Good Manufacturing Practices

Hazard Analysis and Critical Control Points (HACCP) Plan: Documentation or set of documents, prepared in accordance with the principles of HACCP to ensure control of significant hazards in the feed/food business. *(Codex Alimentarius and adapted)*

Hazard Analysis and Critical Control Points (HACCP) System: The development of a HACCP plan and the implementation of the procedures in accordance with that plan.

Hazard: Any biological, chemical (including radiological) or physical agent that has the potential to cause illness or injury in humans or animals. *(21 CFR 507.3 FSMA – CGMP Animal Food)*

Hazard Analysis: The process of collecting and evaluating information on hazards identified in raw materials and other ingredients, the environment, in the process or in the feed, and conditions leading to their presence to decide whether or not these are significant hazards. *(Codex Alimentarius and adapted)*

Labelling: Means the attribution of any words, particulars, trademarks, brand name, pictorial matter or symbol to a feed by placing this information on any medium referring to or accompanying such feed, such as packaging, container, notice, label, document, ring, collar or the Internet, including for advertising purposes. *(Regulation 767/2009/EC in EU)*

Management System: Set of interrelated or interacting elements of an organisation to establish policies and objectives and processes to achieve those objectives. *(ISO 9001:2015)*

Manufacture/production: All operations encompassing receipt of materials, processing, packaging, repackaging, labelling, relabelling, quality control, release, storage, and distribution of products covered by the FAMI-QS scope and related controls.

Microorganism: Any microbiological entity, cellular or non-cellular, capable of multiplication or of transferring genetic material, including viruses, viroids, animal and plant cells in culture. *(EFSA Guidance on the characterisation of microorganisms used as feed additives or as production organisms, June 2018)*

Must: Compliance with a requirement which is mandatory for compliance with this standard (obligation to follow the exact requirement as stated by this document).

Monitor: The act of conducting a planned sequence of observations or measurements of control parameters to assess whether a control measure is under control. (*Codex Alimentarius*)

Operator: The natural or legal persons responsible for ensuring that the requirements of food/feed law are met within the feed business under their control. (*Regulation 178/2002/EC and adapted in EU*)

Organisation: Group of people and facilities with an arrangement of responsibilities, authorities and relationships. (*ISO 9000:2005*)

Plant cells: eukaryotic cells present in green plants, which are the basic unit of life in organisms of the kingdom *Plantae*.

Preventive Action: Action to eliminate the cause of a potential nonconformity or other undesirable potential situation. Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence. (*ISO 9000:2015*)

POA (Point of Attention): control measure or combination of control measures applied to prevent or reduce a significant feed safety issue to an acceptable manner. (*adapted from ISO 22000:2018*)

Pre-requisite Programme (PRP): See 'Good Manufacturing Practices' (GMP).

Procedure: specified way to carry out an activity or a process. Procedures can be documented or not. (*ISO 9000:2015*)

Process: set of interrelated or interacting activities that use inputs to deliver an intended result. (*ISO 9000:2015*)

Production organism: A microorganism that may or may not be modified and used to produce a commercial biological substance in a bioprocess.

Quality: Degree to which a set of inherent characteristics fulfils requirements. (*ISO 9000:2015*)

Raw Material: Any material which enters the manufacturing process of the products covered by the FAMI-QS scope.

Record: Document stating results achieved or providing evidence of activities performed. (*ISO 9000:2015*)

Recombinant DNA: A form of DNA that is created by combining two or more sequences that would not normally occur together. (*EFSA Guidance on the characterisation of microorganisms used as feed additives or as production organisms, June 2018*)

Regulatory Requirement: Obligatory requirement specified by an authority mandated by a legislative body. (*ISO 9000:2015*)

Requirement: Need or expectation that is stated, generally implied or obligatory. (*ISO 9000:2015*)

Reworking/rework: Action on a nonconforming product to make it conform to the requirements. (*ISO 9000:2015*)

Risk: A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard. (*Regulation 178/2002/EC in EU*)

Safety: See 'feed safety'.

Shelf Life: A defined time period for which a product fully complies with its specification, if stored appropriately.

Should: Means "must" and the activities, descriptions or specifications accompanied by the word "should" are intended to be mandatory, unless the manufacturer is able to demonstrate that the activity, description or specification is inapplicable or can be replaced by an alternative which must be demonstrated to provide at least an equivalent level of quality and safety assurance (Operators are obligated to achieve the goal of the Process Document by appropriate means).

Site: Area in which animal feed is handled, together with any immediate surrounding area. (*adapted from PAS 222*)

Specialty Feed Ingredient: Any intentionally added ingredient not normally consumed as feed by itself, whether or not it has nutritional value, which affects the characteristics of feed or animals, animal products and animal performance. (*Codex Alimentarius and adapted*)

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material must conform to be considered acceptable for its intended use. 'Compliance to specification' means that the material, when tested according to the listed analytical procedures, meets the listed acceptance criteria.

Step: A point, procedure, operation or stage in the food chain including raw materials, from primary production to final consumption. (*Codex Alimentarius*)

Sufficient: See "Adequate".

Strain: Genetic variant or subtype of a microorganism (e.g., virus or bacterium or fungus).

Traceability: The ability to trace and follow a food, feed, food-producing animal or substance intended to be, or expected to be incorporated into a food or feed through all stages of production, processing and distribution. (*Regulation 178/2002/EC in EU*)

Undesirable substance: Any substance or product, with the exception of pathogenic agents, which is present in and/or on the product intended for the animal feed and which presents a potential danger to animal or human health or to the environment or could adversely affect livestock production. (*Directive 2002/32/EC in EU*)

Validation of control measures: Obtaining evidence that a control measure or combination of control measures, if properly implemented, is capable of controlling the hazard to a specified outcome. (*Codex Alimentarius*)

Verification: The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine whether a control measure is or has been operating as intended. (*Codex Alimentarius*)

Vulnerability: Activities to understand the exposure to vulnerabilities (as an act of feed fraud) in order to define and implement activities to reduce or mitigate the vulnerabilities.

Where appropriate: See "Adequate".

Yeast: eukaryotic single-celled microorganisms classified as members of the fungus kingdom.

3. HACCP SYSTEM

The HACCP System helps an operator to identify and evaluate the feed safety hazards associated with their product(s) and processes with the view of controlling their occurrence. The system enables the operator to implement, document, control and verify the effectiveness of the control of significant hazards in the feed/food business. The HACCP System is science-based, systematic and should be able to accommodate changes in equipment design, process, procedures and technological developments.

The successful implementation of the HACCP System requires the commitment and involvement of management and personnel with knowledge and/or training in its application. Ongoing training is necessary for all levels of personnel, including managers, as appropriate to the feed business.

3.1. General requirements

The HACCP System needs to identify, evaluate, and control hazards relating to feed safety.

Prior to the application of a HACCP System, prerequisite programmes (PRP) must be in place. They must be well implemented, fully operational and verified, where possible.

It is required for the Operator to have effective Good Manufacturing Practices (GMPs) or PRP in place to manage the daily tasks of good hygienic practice(s). The GMPs are the backbone of any quality or safety system and without these no management program is likely to be successful.

Documents should specify how GMPs are managed. Documented information about verifications and modifications of the GMPs must be maintained.

There is a dedicated chapter for GMPs in the FAMI-QS Code of Practice (Chapter 7) providing requirements with a goal of maintaining feed safety and quality.

3.2. HACCP System

The HACCP System consists of the following 7 principles:

- 1) Conduct a hazard analysis and identify control measures;
- 2) Determine the critical control points (CCPs);
- 3) Establish validated critical limits;
- 4) Establish a system to monitor control of CCPs;
- 5) Establish the corrective actions to be taken when monitoring indicates a deviation from a critical limit at a CCP has occurred;
- 6) Validate the HACCP plan and then establish procedures for verification to confirm that the HACCP system is working as intended;
- 7) Establish documentation concerning all procedures and records appropriate to these principles and their application.

The implementation of the HACCP System follows a logical sequence of 12 steps, including the above 7 principles.

3.3. Assemble a HACCP team and identify the scope (Step 1)

The Operator must form a multi-disciplinary team with a leader (HACCP team leader) that will have responsibility for establishing, developing, implementing, maintaining and reviewing the HACCP System. It is vital that this group has the full support of the top management. The team must include people who are very familiar with the products, processes and associated hazards.

The HACCP team leader must:

- a) appoint (where possible) and manage a HACCP team and organise its work;
- b) ensure relevant training, and periodic retraining of the HACCP team members;
- c) arrange for periodic review of the HACCP plan(s);
- d) report to the top management on the effectiveness of the HACCP programme;
- e) review the corrective actions in case of deviations.

Note: The responsibility of the HACCP team leader may include liaison with external parties on matters relating to the Feed Safety and Quality Management system.

The HACCP team must identify the scope of the HACCP System and the associated prerequisite programmes. The scope must describe which products and processes are covered.

3.4. Describe product(s) (Step 2)

Full and detailed information regarding each product is required in order to assess hazards presented by raw materials, ingredients, process or delivery to the end user. The Operator must consider the requirements referred to in the FAMI-QS Code §8.2. Determination of requirements for products.

3.5. Identify the intended use and users of the product (Step 3)

The product description must detail the target groups for which it is intended. It should specify the animal species, directions for expected use, storage and shelf life guaranteed and other information required for its use or compliance with relevant requirements.

3.6. Construct a diagram of the process flow (Step 4)

The Operator must draw up a process flow diagram for each product group. This diagram should indicate all steps taken to produce the product and should include details of any applicable rework, by-products, intermediate products, storage, transport *etc.* One block in the process flow should reflect each step in the process.

The flow diagram must indicate all inputs, including those of ingredients and feed contact materials, water and air, if relevant. Flow diagrams must, as appropriate, include but not be limited to the following:

- the sequence and interaction of the steps in the operation;
- where raw materials, ingredients, processing aids, packaging materials, utilities and intermediate products enter the flow;
- any outsourced processes;
- where applicable reworking and recycling take place;

- where end products, intermediate products, waste and by-products are released or removed.

The diagram should, while including the necessary details, be clear with unambiguous terms. For the purpose of this document please refer to § 4.2 of this document

3.7. On-site confirmation of the process flow diagram (Step 5)

After the flow chart diagram is drawn up, the Operator must make sure it is accurate by checking it against the actual operating process in its facility. The processing activities must be confirmed against the flow diagram during all stages and hours of the operation and the diagram must be amended where appropriate. The confirmation of the flow diagram must be performed by a person with sufficient knowledge of the processing operation.

3.8. Identify, analyse the hazards and consider any measures to control identified hazards (Step 6/Principle 1)

The Operator must use the diagram to list all potential hazards at each process step. Hazards must be specific and the reason or source for its presence must be described.

- a) *Chemical* (including radiological): Pesticides, lubricants, dioxins, heavy metals, cleaning agents, radionuclides, etc.
- b) *Biological*: Undesirable micro-organisms, pests and parasites etc.
- c) *Physical*: Foreign bodies such as glass, wood, jewellery, stones, etc.

For example, for Step 1, the Operator's first consideration should always be, "*How good is the material being supplied to me?*"

The Operator must consider the chemical (including radiological), biological and physical hazards associated with each material entering on site. Potential chemical (including radiological), biological and physical hazards must be considered for each step in the process, in each case taking the particular circumstances with regard to the step into account.

The hazard analysis consists of identifying potential hazards and evaluating these hazards to determine which of them are significant.

When conducting a hazard analysis, the following must be considered:

- a) hazards associated with producing or processing the type of feed, including its ingredients and process steps;
- b) the likelihood of occurrence of hazards, taking into consideration prerequisite programs, in the absence of additional control;
- c) the likelihood and severity of adverse health effects associated with the hazards in the feed in the absence of control;
- d) identified acceptable levels of the hazards in the feed/food e.g. based on regulation, intended use, and scientific information;
- e) the nature of the facility and the equipment used in making the feed product;
- f) survival or multiplication of pathogenic microorganisms;
- g) production or persistence in feed of toxins (e.g. mycotoxins), chemicals (e.g. pesticides) or physical agents (e.g. glass, metal);

- h) the intended use and likelihood of product mishandling by potential consumers that could render the feed unsafe; and,
- i) conditions leading to the above.

Hazards which are such that their prevention, elimination or reduction to acceptable levels is essential to the production of safe feed (because they are reasonably likely to occur in the absence of control and reasonably likely to cause illness or injury if present) should be identified and controlled by measures designed to prevent or eliminate these hazards or reduce them to an acceptable level.

In some cases, this may be achieved with the application of good manufacturing practices. In other instances, control measures will need to be applied within the process, *e.g.* at critical control points.

3.9. Determine the CCPs (Step 7/Principle 2)

Critical control points are to be determined only for hazards identified as significant based on the result of a hazard analysis.

If a hazard needs a specific control and there is no point further downstream in the process that can reduce it, this step is a Critical Control Point (CCP). If the correct application of the Operator's prerequisite programs or if a subsequent step eliminates, prevents or reduces the hazard to an acceptable level, then the step in question is not a CCP. Useful questions the Operator can ask themselves when establishing CCPs are:

- a) *'If I do not control this hazard, is the safety of the end user compromised?'*
- b) *'If I do not apply controls to this hazard at this step, are there other controls further on in the process that will ensure animal or consumer safety?'*

When assessing whether a control measure can be used at the process step being analysed, it is important to consider:

- Whether a control measure at a step is used in combination with a control measure at another step to control the same hazard; if so, both steps must be considered as CCPs.
- If no control measures exist at any step for an identified significant hazard, then the product or process should be modified.

Examples for the determination of the CCPs are in the decision matrix and decision tree. Other examples may exist for the determination of the CCPs. Any selected methodologies should be adequate for the given Organisation; for example, they should be based on its size and production process(es).

One of the methods is using a **decision matrix** that will help the Operator to decide how significant the potential hazard is and how likely it is to occur. It is based on the concept that the significance is the result of the likelihood that a hazard will occur and the severity of the adverse health effect if it occurs.

Examples are shown below.

Example a)

Significance level 1: no need for measures
 Significance level 2: once-only periodical measures
 Significance level 3: general control measures, control of points of attention
 Significance level 4: specific control measures - control at critical control points (CCPs)

Four significance levels can be determined with the evaluation model.

In the event of significance level 1, no measures are necessary.

In case of significance level 2, periodic measures – often activities to be performed just once or minimal review –

have to be carried out.

Significance level 3 requires general control measures, such as hygiene programs, maintenance and calibration, purchasing procedures, etc.

In the event of risk level 4, specific control measures are necessary for that particular situation.

Significance		Severity/Potential impact				
		Insignificant	Minor	Moderate	Major	Fundamental
Likelihood	Almost certain					
	Likely					
	Moderate					
	Unlikely					
	Rare					

	High significance	CCP
	Significant	POA
	Moderate significance	POA
	Low significance	PRP

Example b)

Another and simpler matrix is shown below:

Significance		Severity		
		Small	Medium	High
Likelihood	High	POA	CCP	CCP
	Moderate	Periodic measures	POA	CCP
	Small	No measures	Periodic measures	POA

A control measure must be determined when the result is a POA.

The number of CCPs will depend on the Operator's HACCP plan.

Once a hazard that needs a specific control is identified, the Operator must identify the process step where the control measure should be associated.

3.10. Establish validated critical limits for each CCP (Step 8/Principle 3)

Critical limits establish whether a CCP is in control, and in doing so, they can be used to separate acceptable products from unacceptable ones. These critical limits must be measurable or observable.

Critical limits for control measures at each CCP must be specified and scientifically validated to obtain evidence that they are capable of controlling hazards to an acceptable level if properly implemented. Validation of critical limits may include conducting studies (*e.g.* microbiological inactivation studies). The Operators may not always need to conduct or commission studies themselves to validate critical limits. Critical limits could be based on existing literature, regulations or guidance from competent authorities, or studies carried out by a third party *e.g.*, studies conducted by an equipment manufacturer to determine the appropriate time, temperature and bed depth for a thermal process.

3.11. Construct monitoring system for the CCP (Step 9/Principle 4)

For each CCP, a monitoring system must be established to demonstrate that the critical limits are under control. The system must include all scheduled measurements or observations relative to the critical limit(s). The monitoring procedures must be able to detect a deviation from the critical limit at the CCP.

Where possible, process adjustments must be made when monitoring results indicate a trend towards a deviation from the critical limit at a CCP. The adjustments must be made before a deviation occurs.

Where possible, monitoring of CCPs must be continuous. If monitoring is not continuous, then the frequency of monitoring must be sufficient to ensure, to the extent possible, that the critical limit has been met and limit the amount of product impacted by a deviation.

The monitoring system must consist of documented information including procedures, instructions and records and should include, but not be limited to, the following:

- a) measurements or observations that provide results within an adequate time frame;
- b) monitoring devices used;
- c) applicable calibration methods;
- d) monitoring frequency;
- e) monitoring results;
- f) responsibilities and authorities for monitoring and evaluation of all data.

When monitoring procedures are based on subjective data, *e.g.*, visual inspection of products and/or processes, they must be supported by clear instructions or specifications. Training must be given to the persons with responsibility for the monitoring activities. The personnel doing monitoring must be instructed on appropriate steps to take when monitoring indicates the need to take action.

The monitoring procedure and frequency of monitoring must be capable of determining when the critical limits have been exceeded in time for the product to be isolated, before it leaves the immediate control of the operator.

Data derived from monitoring must be evaluated by a designated person with knowledge and authority to carry out corrective actions when indicated.

3.12. Determine corrective actions (Step 10/Principle 5)

These are the decisions that must be taken once a critical limit has not been met. For example, a contaminated raw material or finished good may be placed on hold, reworked, destroyed, *etc.* A written procedure must be in place that details how this process should be undertaken and someone must have the responsibility for this process.

Specific written corrective actions must be developed for each CCP in the HACCP system in order to effectively respond to deviations when they occur. When critical limits at CCPs are monitored continuously and a deviation occurs, any product being produced at the time the deviation occurs is potentially unsafe. When a deviation in meeting a critical limit occurs and monitoring was not continuous, Operators must determine what product may have been impacted by the deviation.

A root cause analysis must be conducted where possible to identify and correct the source of the deviation in order to minimise the potential for the deviation to reoccur. A root cause analysis could identify a reason for the deviation that limits or expands the amount of product impacted by a deviation.

Details of the corrective actions, including the cause of the deviation and product disposition procedures, must be documented in the HACCP records. Periodic review of corrective actions must be undertaken to identify trends and to ensure corrective actions are effective.

3.13. Validation of the HACCP Plan and verification procedures (Step 11/Principle 6)

3.13.1. Validation of the HACCP Plan

Before the HACCP plan can be implemented, its validation is needed; this consists of making sure that the following elements together are capable of ensuring control of the significant hazards relevant to the feed business: identifying the hazards, critical control points, critical limits, control measures, frequency and type of monitoring of CCPs, corrective actions, frequency and type of verification and the type of information to be recorded.

Validation of control measures and their critical limits is performed during the development of the HACCP plan.

During the initial implementation of the HACCP system and after verification procedures have been established, evidence must be obtained in operation to demonstrate that control can be achieved consistently under production conditions. Any changes having a potential impact on feed/food safety must trigger a review of the HACCP system, and when necessary a revalidation of the HACCP plan.

3.13.2. Verification procedures

After the HACCP system has been implemented, procedures must be established to confirm that the HACCP system is working effectively. These include procedures to verify that the HACCP plan is being followed and controlling hazards on an ongoing basis, as well as procedures that show the control measures are effectively controlling the hazards as intended. Verification also includes reviewing the adequacy of the HACCP system periodically and, as appropriate, when changes occur.

Verification must be carried out by someone other than the person who is responsible for performing the monitoring and corrective actions.

The frequency of verification activities must be sufficient to confirm that the HACCP system is working effectively. Verification of the implementation of control measures must be conducted with sufficient frequency to determine that the HACCP plan is being implemented properly.

Verification must include a comprehensive review (*e.g.*, reanalysis or an audit) of the HACCP system periodically, as appropriate, when changes occur to confirm the efficacy of all elements of the HACCP system. This review of the HACCP system must confirm that the appropriate significant hazards have been identified, that control measures and critical limits are adequate to control the hazards, that monitoring and verification activities are occurring in accordance with the plan and are capable of identifying deviations, and that corrective actions are appropriate for deviations that have occurred. The review must include confirmation that various verification activities have been executed as intended.

3.14. Establish documentation and record keeping (Step 12/Principle 7)

The HACCP system must be maintained as documented information.

Examples of documentation include:

- HACCP team composition;
- Hazard analysis and the scientific support for the hazards included or excluded from the plan;
- CCP determination;
- critical limit determination and the scientific support for the limits set;
- validation of control measures; and
- modifications made to the HACCP plan.

Examples of records include:

- CCP monitoring activities;
- deviations and associated corrective actions; and
- verification procedures performed.

4. Requirements for Bioprocesses

4.1. Description of the process

Bioprocessing uses biological material or its components to obtain the desired product. Bioprocessing is mainly based on upstream processes to produce biological material (cell culture, fermentation) and downstream processes which include recovery, separation/purification of the desired material/intermediate products, and possible preservation steps such as drying/freeze-drying and formulation.

The typical process consists of production of biological material by microorganisms or cell culture. The microorganism itself can also be the product. The microorganisms are grown (fermented) on raw materials and nutrients such as carbon- and nitrogen sources together with micronutrients. After a growth step, the microorganisms may produce the intended product and then this product is separated from the cells (or cells are opened for intracellular products); when the microorganism is the product, the microorganism is separated from the growth media. After separation (or cell opening) the product is processed in one or more recovery steps (typically by precipitation, filtration, centrifugation, chromatography, *etc.* and or washing of the cells). Finally the product may be formulated by: mixing with stabilizers or attachment to carriers and granulation, spray-drying, freeze-drying, immobilization, *etc.*

Different processes may be used to produce biological products. The flow chart below (4.2) describes a typical set of processes which may be involved in the feed production and the subsequent hazard analysis (4.3) to be part of the HACCP system. In order to further minimise the exposure of an organisation to fraud for products coming from a bioprocess, the table 4.4 outlines additional inputs that an organisation shall consider for their vulnerability assessment. The inputs describe issues relating to the regulatory requirements and raise awareness with regard to strain theft or misuse by non-authorized organisations.

4.2. Flow chart of the process: example



Depository Bank: external or internal

4.3. Hazard Analysis, examples (non exhaustive list)

PROCESS STEPS	PROCESS DESCRIPTION	HAZARD DESCRIPTION	REASON OR SOURCE OF THE HAZARD	EXAMPLES OF CONTROL MEASURES
Production organism(s)/strain(s)	Production organism(s)/strain(s)	Genes of concern (<i>e.g.</i> , toxins, virulence factors, antimicrobial resistance genes)	Production of toxins and virulence factors and occurrence of phenotypic antimicrobial resistance caused by improper characterization of the strain and/or by the use of an unwanted/incorrect strain.	<p>Purity and strain identity check prior to the use, through established internal procedure.</p> <p>Yield check (against internal established levels) and morphology check (comparing sample with reference sample, via microscopy) during fermentation. Name and strain number obtained from an official depository authority where required by law (proved via a copy of official certificate) and legislation of destination countries.</p> <p>Control/prevention:</p> <p>Strain characterization based on whole genome sequencing and analysis supported by phenotypic characterization.</p>
		Chemical/biological hazards	Mix-up or contamination of production strain.	<p>Depository cell bank and purity check procedures.</p> <p>Yield check during fermentation.</p>
	Selection of raw materials for processing	Heavy metals, dioxins, pesticides, radionuclides, etc.	<p>Unwanted chemicals from raw materials due to contamination or wrong grade of raw materials.</p> <p>Radionuclides resulting from accidental contamination, <i>e.g.</i>, contamination arising from accidental release from a nuclear facility or from</p>	<p>Supplier and raw materials assessment combined with receiving inspection, periodic analysis and process controls like sieving and infection control.</p> <p>Monitoring of accidental releases of radiological hazards and verification of the possible impact on raw</p>

PROCESS STEPS	PROCESS DESCRIPTION	HAZARD DESCRIPTION	REASON OR SOURCE OF THE HAZARD	EXAMPLES OF CONTROL MEASURES
			damage to a nuclear facility from a natural disaster.	materials during its manufacturing, storage, transport.
		Object in raw materials	Piece of equipment/supplier control measures insufficient.	Sieving
		Pathogenic microorganisms and/or toxins	Raw materials contaminated with pathogenic and/or toxin producing organisms.	Supplier and raw material assessment
Fermentation/Biomass production	Propagation of production strain(s) and formation of the intended product in growth medium	Pathogenic microorganisms/toxins	Growth of pathogenic/toxin forming organisms during the fermentation.	Procedures to avoid and/or check for any contamination (<i>e.g.</i> , sterilization, hygienic procedures, maintenance of equipment).
		Degradation of the intended product(s)	Degradation of intended product(s) into undesirable substances.	Control of the process to ensure repeatability; Monitoring of product stability and undesirable substances.
		Heavy metals, plastic monomers Parts and pieces	Chemical or physical contamination from equipment including contaminants from wear and tear (pieces of glass, metals, etc.), migration of metals and plastic monomers from contact materials.	Preventive maintenance programme (preventive maintenance programme and analyses), sieves. Selection of suitable contact materials.
Separation of product/microorganism and Recovery/Purification	Separation of intended product from the rest of the broth (production organism, organic and inorganic growth medium)	Gene(s) of concern or viable cells from production strain(s) in the final product	If the production organism contains gene(s) of concern or is classified as Biological safety level II: presence of gene(s) of concern or of cells of the organism(s) in the final product.	Procedures to measure the absence of viable cells from production strain(s) (<i>by e.g.</i> , plating). Analytical methods (<i>e.g.</i> PCR methods) to confirm absence of gene(s) of concern in final intended product(s).
		Pathogenic microorganisms	Growth of contaminating microorganisms due to favourable pH and temperature conditions.	Heat treatment/sterilization of equipment/cleaning in place/pH/temperature conditions; monitoring and verification to ensure sterile conditions.

PROCESS STEPS	PROCESS DESCRIPTION	HAZARD DESCRIPTION	REASON OR SOURCE OF THE HAZARD	EXAMPLES OF CONTROL MEASURES
				Procedure of inoculation of fermentor to ensure no contamination.
		Pathogenic microorganisms Toxins	Contamination with pathogenic and/or toxin-producing organisms from environment, personnel or pests during handling and/or opening.	Product processing procedures including handling, opening and personal hygiene, disease control, pest control, contamination checks, environmental control. COA, supplier assessment. Drying step.
		Physical, chemical, biological hazards from utilities (water supply or other solvents, steam, air...)	Contamination from cleaning agents, lubricants, utilities (water, steam, air). Chemical or physical contamination from equipment, including wear and tear (pieces of glass, metals, and migration of metals and plastic monomers from contact materials (also during intermediate storage). Contaminants from cleaning agents, lubricants, process air, utilities. Contaminants from the water used.	Preventive maintenance programme (e.g., to prevent oil leaks). Requirements for utilities (filtering of air, use of oil suitable for feed products etc.), including analyses of water (well or municipal), water use for steam and growth medium on a regular basis. Analyses or verification of reports on water source (well or municipal) and other solvents on a regular basis. Cleaning programme.
Formulation	Formulation with additives, stabilizer, aids, carriers, preservatives etc. Granulation	Physical, chemical, biological hazards from utilities (water supply or other solvents, air...)	Contaminants from the water used, air, solvents.	Utilities requirements (filtering of air, use of oil suitable for feed products etc.).
				Analyses or verification of reports on water source (well or municipal) and other solvents on a regular basis.
				Preventive maintenance programme. Use of food grade lubricant/grease.

PROCESS STEPS	PROCESS DESCRIPTION	HAZARD DESCRIPTION	REASON OR SOURCE OF THE HAZARD	EXAMPLES OF CONTROL MEASURES
		Parts and pieces, debris	Physical contamination from equipment, personnel, pests or birds during handling and opening.	Processing procedures and personal hygiene, pest control, contamination checks, maintenance programmes.
		Pathogenic microorganisms Toxins	Contamination from pathogenic and/or toxin producing organisms from environment, personnel or pests.	
		Undesirable substances, carry-over residues	Chemical contamination of formulation chemicals (e.g., with mycotoxins, heavy metals, dioxins etc.).	Preventive measures to control carry-over, cleaning, CIP and analyses.
		Ingredient/agent above or below the acceptable level	Non-uniform distribution of ingredients/raw material.	Validation and regular testing of the mixer/mixing efficiency.
Packaging and Labelling	Packaging of the products in bags, boxes, drums, etc.	Microorganisms, chemical substances from packaging	Contaminants from unsuitable packaging (e.g., not suited for feed products). Migration tests of packaging materials.	Selection of suitable packaging/risk analyses of packaging materials.
		Foreign material	Contamination with foreign material during the packaging process.	Packaging via dedicated production lines and packaging machines (metal detection). Cleaning and inspection procedures. Usage of new and/or clean packaging materials.
	Products in bulk	Physical, chemical and biological hazards	Physical, chemical and biological hazards from previous loads, dirty tanks, dirty silos.	Transport certification. Cleaning/inspection of bulk transport. Use of dedicated transport.

PROCESS STEPS	PROCESS DESCRIPTION	HAZARD DESCRIPTION	REASON OR SOURCE OF THE HAZARD	EXAMPLES OF CONTROL MEASURES
	Identify the products with the right label identification according to the applicable legislation and to be able to track and trace the products in case it is necessary	Wrong product packaged/labelled	Inaccurate labelling and identification of the product leading to improper usage of the product or inability to do a complete recall in case of incident.	Labelling procedures.
				Batch identification system check.
				Labelling identification, label inventory.
		Degradation substances	Storage under temperatures that lead to premature product deterioration.	Temperature control to prevent microbial growth.
Warehousing procedures to ensure hygiene and temperature control according to recommended storage conditions.				
Shipment of packed goods or in bulk	Shipment of packed goods	Foreign materials, pests or residues from other products	Possible contamination with foreign materials, pests or other goods in case the packaging gets damaged.	Communication to the transport/ logistic organization of the necessary requirements e.g.: temperature, hygiene.
				Inspection before loading /dedicated transport.
				Notification of any problems during transport.
	Bulk shipment	Foreign materials, residues from other products	Possible contamination from previous loads.	Contractual agreements with transporters to ensure hygiene and temperature control according to the recommended transport conditions.
				Check of cleaning certificates.
				Inspection before loading/dedicated transport.
				Info about previous load(s) and request for cleaning certificates.

4.4. Inputs for the Vulnerability Assessment

The below table does not comprise a complete vulnerability assessment as described in the FAMI-QS Feed Fraud Prevention and Defence Module <https://fami-qs.org/feed-fraud-prevention-and-defence-module.html>. The points described in the below table shall be considered as additional inputs, with regard to the regulatory requirements, when applicable, to the vulnerability assessment of the FAMI-QS Feed Business Operator and be discussed with the fraud team.

PROCESS STEPS	PROCESS DESCRIPTION	DESCRIPTION OF POINT OF INTEREST	EXAMPLE OF CHECKS
Production organism/strain	Production organism/strain	Selection of a non-compliant strain (for the intended use or non-authorised in the country where the product is placed on the market).	Check of regulatory status of the microorganism(s) (according to applicable regulation of the country where the product is to be placed on the market, <i>e.g.</i> reference to an application dossier and regulation of authorisation when applicable). Verification that the microorganism used in production and the one stated in the approval and/or licence letter are in alignment.
	Selection of raw materials for processing	Selection of non-compliant raw materials or processing aids.	Consideration of the respective regulatory framework in the country where the product is to be placed on the market.
PROCESS STEPS	PROCESS DESCRIPTION	DESCRIPTION OF POINT OF INTEREST	EXAMPLE OF CHECKS
Separation of product/microorganism and Recovery/Purification	Separation of the intended product from the rest of the broth (production organism, organic and inorganic growth medium)	Presence of recombinant DNA or cells of the production strain in final intended product(s), if applicable.	Absence of detectable recombinant DNA by methods according to requirements in the country where the product is to be placed on the market. Confirmation of the absence (<i>e.g.</i> plating) of viable cells of the production strain.
Formulation	Formulation of feed additives with formulation aids, carriers, preservatives <i>etc.</i> Granulation	N/A (see raw materials)	Consideration of the regulations in the country where the product is to be placed on the market.
PROCESS STEPS	PROCESS DESCRIPTION	DESCRIPTION OF POINT OF INTEREST	EXAMPLE OF CHECKS
Packaging and Labelling	Packaging of the products in bags, boxes, drums, <i>etc.</i>	Packaging not compliant with feed legislation.	Consideration of the regulations in the country where the product is to be placed on the market.
	Identify the products with the right label identification according to the applicable legislation	Innaccurate labelling and identification of the product leading to non-compliant usage of the product.	Consideration of the regulations in the country where the product is to be placed on the market.
Storage and Transport	Storage and transport of products	Non-compliant storage and transport rules.	Consideration of the regulations in the country where the product is to be placed on the market.

5. Inputs for the management of process and strain changes

Change(s) to the microbial (production) strain as well as its use in the manufacturing process of a speciality feed ingredient require(s) additional consideration, as outlined below. In addition to the typical change control evaluation, there should be an assessment of the biological material modification since it may introduce additional changes which may impact the final product.

Aspects for further consideration in line with the FAMI-QS Code include:

FAMI-QS Code §5.2 Responsibilities

Given the potential impact of a microbial (production) strain change and or a change in the manufacturing process due to this change, the interdisciplinary team and/or the HACCP team responsible for evaluating the change should also include an individual with expertise in microbiology and/or molecular biology who should analyse the potential impact on product conformity and its safety.

FAMI-QS Code §8.4 Change control

Impact on the manufacturing process and on the product conformity and safety because of a strain change should be documented. This documentation should include, where relevant:

- Summary of theoretical considerations about the nature of the strain change and the associated hazards, and experimental data confirming the safety of the strain and/or product assessment of risks and mitigation
- Potential impact on the final product
- Regulatory compliance, both in country of production and where the product is placed on the market, including compliance with the registered specifications.

6. References – Guidance

General principles of Food Hygiene (CXC/RCP 1 – 1969, Rev 2020. Annex on Hazard Analysis Critical Control Point (HACCP) System and Guidelines for its Application): <http://www.fao.org/fao-who-codexalimentarius/>

- ICH Q6B: <https://www.ich.org/>
- QPS-Qualified Presumption of Safety: <https://www.efsa.europa.eu/en>
- GRAS-Generally Recognized as safe: <https://www.fda.gov/>

The European Commission has established the European Union Register of Feed Additives, which is regularly updated, and it makes reference/links to the relevant authorisation Regulations. Those Regulations include the specific requirements for placing the additives on the EU and EEA market https://ec.europa.eu/food/safety/animal-feed/feed-additives/eu-register_en.