INTERNATIONAL FOOD ADDITIVES COUNCIL QUALITY SYSTEMS, FOOD SAFETY AND GOOD MANUFACTURING PRACTICES GUIDE FOR FOOD ADDITIVES AND GRAS SUBSTANCES

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Table of Contents

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This Guide was prepared by the International Food Additives Council (IFAC) through its Food Safety Committee. IFAC is a global association representing manufacturers and users of food ingredients, including food additives and GRAS substances. IFAC strives to promote science-based regulations, standards and specifications for food ingredients worldwide.

INTERNATIONAL FOOD ADDITIVES COUNCIL QUALITY SYSTEMS, FOOD SAFETY, AND GOOD MANUFACTURING PRACTICES GUIDE FOR FOOD ADDITIVES AND GRAS SUBSTANCES

This document represents voluntary guidelines for the food additive and GRAS substances industry and the contents should not be interpreted as regulatory requirements. Its purpose is to provide guidelines on Quality Systems, food safety principles and Good Manufacturing Practices that are more applicable to the food additive and GRAS substances segment of the overall food industry, and may provide a unified approach to these principles for the international food additive and GRAS substances industry.

1. INTRODUCTION

The U.S. FDA Food Safety Modernization Act (FSMA), enacted in January 2011, fundamentally shifts the focus of food safety in the United States from responding to food safety incidents after they occur to preventing them from happening. FSMA applies to the safe production of all foods sold in the U.S., including agricultural products, raw materials, processed foods, food additives and GRAS substances, and includes requirements for appropriate Quality Systems, Preventive Controls and Good Manufacturing Practices (GMPs) during product manufacture, transport and storage. These requirements appear in the U.S. Code of Federal Regulations at Title 21, Part 117 (21 CFR Part 117) and remain consistent with Current Good Manufacturing Practice (CGMP) requirements followed by industry that existed prior to FSMA.[1]

1.1 Purpose and Scope

The purpose of this Guide is to provide guidelines for industry on Quality Systems, food safety principles, GMPs, and Quality Assurance Principles that are applicable to the safe manufacture of food additives and GRAS substances and in accordance with FSMA as well as preceding CGMP requirements. As this Guide represents the International Food Additives' (IFAC) interpretation of FSMA, it is also intended to provide a unified approach to these principles for use by the international food additive and GRAS substance industry.

The Guide is applicable to the manufacture of food additives and GRAS substances intended for use in food as well as dietary supplements (i.e., ingredients used in products complying with 21 CFR 111). It covers the quality management system and GMPs necessary throughout manufacturing for both batch and continuous processes. It is intended to assist both manufacturers and auditors in establishing whether the facilities and controls used for the safe manufacture of food additives and GRAS substances are adequate to ensure food safety per existing laws and regulations.

It should be noted that this Guide provides what IFAC believes are best practices, and in some cases provides recommendations which are beyond FSMA requirements. Although this document summarizes FSMA requirements, it does not guarantee legal compliance with FSMA or other international food safety regulations and some topics may warrant further research dependent on the unique qualities and location of the manufacturer of interest as noted in Sections 1.2.1 and 1.2.2. Interested bodies should understand the applicable laws and regulations within each country and ensure compliance accordingly.

In addition to FSMA and IFAC's industry best practices provided in this document, guidelines and specifications to address the purity of food additives and GRAS substances are provided by the Food Chemicals Codex[2], the Codex Alimentarius, the European Commission[3-4] and others.

In addition, some of the fundamental quality systems in use for all types of industries is ISO-9001, ISO-22000, and the Global Food Safety Initiative (GFSI). ISO-9001 provides a framework and support for development and continuous improvement of all aspects of quality related activities. ISO-22000 consists of a series of internationally developed standards to address food safety management and food safety systems. GFSI is a series of food safety certification programs, including FSSC-22000, which were established to ensure confidence in the delivery of safe food, while improving safety throughout the supply chain. GFSI standards address food, packaging, packaging materials, storage and distribution for primary producers, manufacturers and distributors. This Guide therefore provides *specific* guidelines for the international food additive and GRAS substances industry, utilizing aspects and concepts of these other standards, and may be used to supplement the regulations applicable in a country or region.

1.2 Principles Adopted

1.2.1 The Guide and its Use

Food additives and GRAS substances represent a diverse group of materials and often have uses other than in traditional food applications. Each manufacturer shall consider how this Guide might apply to its individual products and manufacturing processes, including whether some principles may not be applicable to certain products and processes.

The term "should" as it is used in this Guide indicates IFAC's recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative that provides at least an equivalent level of quality assurance. Note that "should" does not mean "must" or "shall." In cases where certain practices or activities are required by U.S. law, shall or must is used.

References to FSMA are used throughout this Guide to indicate requirements for food additives and GRAS substances manufactured in the U.S. or for the U.S. market. Specific FSMA requirements may not be applicable to food additives and GRAS substances intended for other markets, but many FSMA concepts are still generally applicable to the safe production of food additives and GRAS substances.

1.2.2 Application

The text provides guidelines necessary for the safe manufacture of food additives and GRAS substances but may not include all of the details, practices or activities that are needed to ensure safety in all cases. As an international guideline, it does not specify national legal requirements or cover particular characteristics of every food additive

and GRAS substance. Manufacturers should consider all relevant local, national and international regulations covering their products to ensure compliance. The Guide may, however, be useful in providing guidelines specific to food additive and GRAS substance manufacturing as compared with more general GMPs that are designed for all foods.

Sections 4 to 7 provide guidelines on the quality management systems, food safety principles, and GMP practices suitable for the safe manufacturing of food additives and GRAS substances. For example, these sections recommend measures to limit food additive and GRAS substance contamination. No attempt has been made to include details specific to any particular food additive or GRAS substance. Individual manufacturers should assess the potential hazards and risks associated with the manufacture of their products and apply appropriate systems to mitigate those potential hazards and risks.

The Appendices contain a Glossary and Bibliography.

1.2.3 Quality System

The quality management system standards chosen as a framework for this Guide include the current versions of ISO 9001 and GFSI standards (e.g., ISO-22000). A manufacturer may apply ISO standards or other similar appropriate standards with or without certification.[6] Pursuit of a certification is a business decision and not addressed in this Guide. However, certification to internationally recognized and accepted quality programs has the benefit of providing assurance to customers that the food additive and GRAS substance manufacturer's quality management system has been independently verified.

1.2.4 Hazard Analysis and Risk-Based Preventive Controls

FSMA amends the U.S. Federal Food, Drug, and Cosmetic Act with respect to food safety with a focus on risk-based preventive controls intended to prevent food safety incidents. Aspects of FSMA relevant for quality management are addressed in the appropriate sections below. ISO-9001 and GFSI are also risk-based and preventative approaches to quality systems. A strong management and leadership based approach to quality systems and food safety programs is essential and are common themes among all of these systematic approaches. As noted above, compliance with FSMA is not applicable to products not intended for sale in the U.S. However, FSMA's preventive approach and risk-based controls paradigm is applicable generally to the production of all food additives and GRAS substances.

2. DEFINITIONS

(SEE APPENDIX A)

3. GENERAL GUIDELINES

The application of quality systems, food safety programs and GMPs are relevant once a manufacturer has determined that a substance is intended for use as a component of a food or a non-active component of a dietary supplement. Manufacturing of food additives and GRAS substances in the U.S. or when those products are intended for the U.S. market shall be carried out in accordance with

21 CFR Part 117, and in compliance with appropriate quality systems and GMP principles consistent with this Guide.

The objective of food additive and GRAS substance quality programs, including GMPs, is to ensure that the manufacture of a food additive or GRAS substance results in a material that is safe, is not contaminated or adulterated, is prepared, packed and stored under sanitary conditions, meets desired quality characteristics and is fit for its intended use. In addition, suitable procedures and records must be available for review, with internal evaluation and verification practices in place.

The emphasis of the food safety program is a systematic risk-based approach for managing hazards to assure product integrity and customer satisfaction. Manufacturing processes shall be controlled and documented. Hazard analysis and risk-based preventive control systems, such as Hazard Analysis and Critical Control Points (HACCP) or FSMA Preventive Controls, should be developed and implemented in accordance with the specific requirements and relevant guidelines consistent with the associated risk level and based on a thorough knowledge of the process. Hazard analyses should be science-based, well documented and available for review during audits. A written hazard evaluation and risk assessment plan shall be developed and incorporated into the quality system.

4. QUALITY MANAGEMENT SYSTEM-FOOD ADDITIVE GRAS SUBSTANCE QUALITY SYSTEMS

4.1 General Requirements

The principles outlined in this Guide provide a comprehensive basis for the development and implementation of a quality management system appropriate for the manufacture of food additives and GRAS substances. Food additive and GRAS substance manufacturers should identify the quality management processes required to assure quality.

Where manufacturing, testing or other operations that could affect food additive and GRAS substance quality may be outsourced, the responsibility for quality remains with the food additive and GRAS substance manufacturer and control measures should be well defined by the manufacturer (see also Section 7).

4.2 Documentation Requirements

4.2.1 General

The food additive and GRAS substance manufacturer must have a system in place to control required documents and data that relate to quality management and preventive control systems, such as HACCP, FSMA Preventive Controls and food defense. The food additive and GRAS substance manufacturer should also adhere to the following principles:

- Conduct a hazard analysis;
- Identify appropriate controls, e.g., Critical Control Points or FSMA Preventive Controls;
- Establish critical limits;
- Establish monitoring requirements;
- Establish corrective actions;
- Establish recordkeeping procedures; and
- Establish procedures for verifying the system is working as intended.

For products manufactured in the U.S. or intended for the U.S. market, the hazard analysis must be used to develop a written food safety plan as required by 21 CFR 117, Subpart C.

4.2.2 Written Plan and Documentation of Preventive Controls

The food additive and GRAS substance manufacturer shall have a written plan that documents and describes the procedures used by the facility to comply with food safety standards, such as analyzing the hazards as required by 21 CFR 117.130 and identifying preventive controls to address those hazards as required by 21 CFR 117.135.

The food additive and GRAS substance manufacturer must maintain a copy of the facility's written food safety plan. It must also maintain, for at least two years, records of monitoring, instances of non-conformance material to food safety, corrective actions, verification activities and the efficacy of preventive controls and corrective actions. In the U.S., such records must be made available to the U.S. FDA promptly upon oral or written request.

The food additive and GRAS substance manufacturer must reevaluate each facility's food safety plan at least every three years. Within each food safety plan, preventive controls must also be reevaluated whenever a significant change is made that creates a reasonable potential for a new hazard or a significant increase in a previously identified hazard.

4.2.3 Quality Manual

The food additive and GRAS substance manufacturer should prepare a quality manual describing the quality management system, the quality policy and the commitment of the food additive and GRAS substance manufacturer to applying the appropriate GMPs, quality management standards and preventive controls contained in this Guide to ensure food safety. This manual, which can be a single document or an inventory of materials, should include the scope of the quality management system, reference to supporting procedures (e.g., written operational instructions for laboratory test methods, documentation of validation studies pertaining to laboratory test methods) and a description of the interaction between quality management processes.

4.2.4 Control of Documents

The food additive and GRAS substance manufacturer should establish and maintain procedures for the identification, collection, indexing, filing, storage, maintenance and disposition of controlled documents, including documents of external origin that are part of the quality management system.

Procedures used in the manufacture of food additives and GRAS substances should be documented, implemented and maintained. In addition, there should be formal controls relating to procedure approval, revision and distribution. These controls should provide assurance that the current version of a procedure is being used throughout the operational areas and previous revisions of documents have been removed.

Documents and subsequent changes to documents should be reviewed and approved by designated qualified personnel before issuance to the appropriate areas, as

identified in the documents. Documents that impact product quality should be reviewed and approved by the quality unit (see also Section 4.4.5).

Controlled documents should include a unique identifier, date of issue and revision number to facilitate identification of the most recent document. The department with the responsibility for issuing the documents should be identified. Where practical, changes and the reasons for the changes should be documented.

Electronic documentation should meet the requirements for the document control system stated above. If electronic signatures are used on documents, they should be controlled to provide equivalent security to that given by a handwritten signature. Electronic documents and signatures may also need to satisfy local regulatory requirements.

4.2.5 Control of Records

The food additive and GRAS substance manufacturer should establish and maintain procedures for the identification, collection, indexing, filing, storage, maintenance and disposition of records. FSMA recordkeeping requirements are found in a variety of sections in 21 CFR 117, Subparts C and F.

Records should be maintained to demonstrate achievement of the required quality and the effective operation of the quality management system. Records should be legible and identifiable with the product involved. Pertinent subcontractor quality data should be an element of these records.

Entries in records should be clear, indelible, made directly after performing the activity (in the order performed), signed and dated by the person making the entry. Corrections to entries should be signed and dated, leaving the original entry legible.

The food additive and GRAS substance manufacturer shall maintain, for not less than two years, records documenting the monitoring of the preventive controls implemented, instances of non-conformance material to food safety, the results of testing and other appropriate means of verification, instances when corrective actions were implemented and the efficacy of preventive controls and corrective actions. If records are stored offsite, they should be stored and maintained in such a manner that they are readily retrievable within 24 hours of request for official review and in facilities that provide a suitable environment to minimize deterioration or damage. The food safety plan must remain onsite.

4.3 Change Control

The manufacturer shall establish and maintain procedures to evaluate and approve changes that may have an impact on the quality, safety or technical function of the food additive or GRAS substance. For example, this may include changes to:

- Raw materials or packaging;
- Material specifications;
- Test methods;
- Manufacturing equipment;
- Production processes; and
- Manufacturing or packaging sites, etc.

Documents including written plans should be revised accordingly. If no additional or revised preventive controls are needed, then this too should be documented. A function that is independent from production (such as regulatory affairs, quality assurance, etc.) should have the responsibility and authority for the final approval of changes. Changes must be evaluated for effectiveness and the impact on food safety and quality.

The change control process should consider the significance of the change and if customer notification is required (see also Section 6.2.3).

4.4 Quality Management

4.4.1 Management Commitment

Management should demonstrate to the organization the importance it places on customer satisfaction and compliance with the appropriate regulations and standards. This should be accomplished through the development of a quality policy and establishment of quality objectives. Progress towards the documented quality objectives should be reviewed for effectiveness at planned intervals.

4.4.2 Customer Focus

It is the responsibility of management to ensure that customer requirements are determined and met.

The food additive and GRAS substance manufacturer should permit the customer or third party to conduct audits to review its quality management system, manufacturing processes, buildings and facilities.

Manufacturers should implement a system for monitoring customer satisfaction and taking appropriate action where indicated.

4.4.3 Quality Policy

Management should demonstrate its commitment to the corporate quality policy and ensure that it is implemented within the operational unit. The quality policy should support continual improvement of the quality management system and a commitment to food safety. Management should participate in the development of the company's quality policy and provide the resources necessary for its development, maintenance and deployment.

4.4.4 Hazard Analysis and Risk-Based Preventive Controls

4.4.4.1 Hazard Analysis

In the interest of food safety, the facility shall evaluate the hazards that could reasonably be foreseen to affect the food additive and GRAS substance manufactured, processed, packed or held by the facility, and identify and implement preventive controls, where applicable. The objective is to ensure that the food additive and GRAS substance is not adulterated or misbranded.

4.4.4.2 Hazard Identification and Mitigation

The manufacturer shall:

- Identify and evaluate known or reasonably foreseeable hazards that may be associated with the facility which may have an effect on food safety, including:
    - biological, chemical, physical, and radiological hazards, including but not limited to: natural toxins, pesticides, drug residues, decomposition, parasites, allergens, and approved food and color additives; ; and
    - hazards that occur naturally, or may be unintentionally introduced, or may be intentionally introduced for purposes of economic gain;
- Document hazard analysis (as required under 21 CFR 117.130(a)(2)) and develop and implement preventive controls (as required under 21 CFR 117.135(b));
- Provide resources to implement these plans and written verification programs (as required by 21 CFR 117.165(b)); and
- Develop a written program outlining the system to monitor the preventive controls (as required by 21 CFR 117.145 and 21 CFR 117.165).

Where appropriate, the manufacturer should also:

- Develop a written supply chain management program (as required under 21 CFR Part 117, subpart G));
- Develop a written recall program (as required under 21 CFR 117.139(a));

4.4.5 Planning

4.4.5.1 Quality Objectives

Management should set objectives for adherence to quality systems, food safety programs and GMPs to ensure that the food additive or GRAS substance is safe and the manufacturer maintains and improves its performance. Objectives should be deployed throughout the organization and should be measurable and consistent with the quality policy.

4.4.5.2 Quality Management System Planning

Management should provide adequate resources to ensure conformance to the provisions of this Guide. There should be a process for the identification of resources needed for adherence to GMPs. Management should ensure that the integrity of the quality management system is maintained when changes are planned and implemented.

4.4.6 Responsibility and Authority

Management should define individual(s) who have the responsibility and authority to:

- Ensure quality-critical activities are undertaken as defined;
- Develop and enforce a quality plan to approve or reject raw materials, packaging components, intermediates and finished products, and oversee proper review of production records to ensure that significant deviations are investigated;

- Participate in reviewing and authorizing changes to processes, specifications, procedures and test methods that potentially affect quality and in investigating failures and complaints;
- Ensure conformance with regulatory requirements; and
- Develop and implement a self-inspection program of the quality management system.

The individual(s) delegated by management with oversight for development and review of the food safety plan shall be qualified by relevant experience or training which is documented in writing. For food additives and GRAS substances manufactured in the U.S. or for the U.S. market, this individual(s) must prepare or oversee the preparation of the food safety plan as required under 21 CFR 117.126(a)(2) and meet the definition of the preventive controls qualified individual (PCQI) established in 21 CFR 117.3.

The food additive and GRAS substance manufacturer may delegate activities to other qualified personnel if appropriate controls (e.g., periodic audits, training and documentation) are in place.

Personnel who have an impact on food additive and GRAS substance quality should have job descriptions that specify their role in the responsibility of practicing food additive and GRAS substance quality systems, food safety programs and GMPs. Any individuals engaged in the manufacturing, processing, packing or holding of food additives and GRAS substances shall have documented training or experience commensurate with their responsibilities that includes the principles of food hygiene and food safety (per 21 CFR 117.4).

4.4.6.1 Internal Communication

The food additive and GRAS substance manufacturer should ensure appropriate systems are established to communicate GMPs and regulatory requirements, food safety, quality policies, quality objectives and procedures throughout the organization. The communication should also provide information about the effectiveness of the quality management system.

Management should be notified in a timely manner of quality-critical situations (especially issues that may impact the safety of the food supply) in accordance with a documented procedure.

4.4.6.2 Recalls

There should be a written procedure that defines the circumstances under which a recall of a food additive or GRAS substance should be considered. The recall procedure must designate who should be involved in evaluating the information, how the recall should be initiated, who should be informed about the recall and how the recalled material should be treated. In event of a serious or potential life threatening situation, the information should be entered into the reportable food registry. In addition, local, national and/or international authorities should be informed and their advice sought.

In the event of a recall, the manufacturer shall conduct an effectiveness check to verify that the recall was carried out and ensure the proper disposition of the recalled material (per 21 CFR 117.139).

Manufacturers should conduct mock recalls (see Section 6.5.3).

4.4.7 Management Review

4.4.7.1 General

Management should hold periodic reviews of the quality management system and preventive controls program to monitor and confirm the organization's continued conformance to this Guide and to preventive controls principles.

The review should be recorded and include assessing opportunities for improvement and the need for changes to the quality management system and preventive controls program.

4.4.7.2 Review Input

Management review inputs should include, for example:

- Results of internal and external audits;
- Customer feedback of the company performance;
- Product conformity and process performance;
- Action items from the previous management review;
- Customer complaints;
- Status of corrective or preventive actions; and
- Changes that could affect the quality management system.

4.4.7.3 Review Output

Management review should identify the resources needed and opportunities presented for improvement of the quality management system and improvement of product conformance to customer and regulatory requirements. A record should be made of actions recommended and taken.

5. PERSONNEL AND RESOURCE MANAGEMENT

5.1 Provision of Resources

There should be sufficient qualified personnel and resources (e.g., equipment, materials, buildings and facilities) to implement, maintain and improve the quality management system and to produce, package, test, store and release each food additive or GRAS substance in a manner consistent with this Guide.

5.2 Personnel

5.2.1 General

Personnel performing work affecting the quality of food additives and GRAS substances shall have the appropriate combination of education, training and experience for their assigned tasks. (See also Section 4.4.6.)

Consultants advising on the design, production, packaging, testing or storage of food additives and GRAS substances should have sufficient education, training and experience or any combination thereof to advise on the subject for which they are retained. Records should be maintained listing the name, address and qualifications of consultants and the type of service they provide.

5.2.2 Competence, Awareness and Training

The food additive and GRAS substance manufacturer should establish and maintain procedures for identifying training needs and providing the necessary training to personnel performing activities affecting food additive and GRAS substance quality.

Appropriate records of training should be maintained, such as dates of training, type of training and personnel trained. Training should address the particular operations that the employee performs, such as GMPs, hazard analysis, and food defense as they relate to the employee's functions.

Staff with responsibilities for quality system, food safety and GMP programs shall conduct and document training with sufficient frequency to ensure that employees remain familiar with applicable principles. Management shall establish adequate and continued personal hygiene training for personnel who handle materials so that they understand the precautions necessary to prevent contamination of food additives and GRAS substances.

The training program should ensure that personnel understand that deviations from procedures may have an impact on the safety of the product and/or product quality.

Appropriate assessment of training or existing qualifications should be documented in writing.

5.2.3 Personnel Hygiene

To protect food additives and GRAS substances from contamination, protective apparel such as head, face, hand and arm coverings should be worn as appropriate to the duties performed. Jewelry and other loose items, including those in pockets, should be removed or covered. Only authorized personnel should enter those areas of the buildings and facilities designated as limited access areas.

Personnel should practice good sanitation and health habits, such as frequent handwashing. Any person shown to have an apparent illness or open lesions (by either medical examination or supervisory observation) that may adversely affect the safety or quality of the food additive or GRAS substance should be excluded from direct contact with raw materials, packaging components, intermediates and finished food additives and GRAS substances until the condition is corrected or determined by competent personnel not to jeopardize the safety or quality of the food additive or GRAS substance. Personnel should be instructed to report to supervisory personnel any health conditions that may have an adverse effect on food additives and GRAS substances.

The storage and use of food, drink, personal medication (unless otherwise authorized), tobacco products or similar items should be restricted to certain designated locations separate from manufacturing areas.

5.3 Facility Infrastructure

Facility infrastructure should be managed, operated, cleaned and maintained in accordance with GMP principles to ensure food additive and GRAS substance quality and to avoid contamination (including, where critical to food additive and GRAS substance quality, control of particulate matter, microbiological control and control of water quality).

An appropriate risk assessment of the facility grounds should be conducted. Plants should be designed or managed in a way that minimizes contamination of the product. Activities to minimize hazards associated with the plant grounds include but are not limited to:

- Adequate maintenance of plant grounds;
- Eliminating breeding and harboring spots for pests on plant grounds;
- Maintaining roads and walkways to eliminate sources of contamination;
- Adequate drainage to prevent seepage and breeding areas for pests;
- Appropriate waste treatment and disposal methods; and
- Preventing contamination coming from neighboring site(s).

5.3.1 Buildings and Facilities

The prevention of contamination should be considered in the design of the manufacturing processes and facilities, particularly where the food additive and GRAS substance is exposed. Buildings and facilities used in the production, processing, packaging, testing or storage of a food additive and GRAS substance should be maintained in a good state of repair and should be of suitable size, construction and location to facilitate cleaning, maintenance and correct operation appropriate to the type of processing.

Manufacturing processes associated with the production of highly sensitizing or toxic products (e.g., herbicides, pesticides, etc.) should be located in dedicated facilities or use equipment separate from that used for food additive and GRAS substance manufacture. If this is not possible then appropriate measures (e.g., cleaning) should be implemented and documented to avoid cross-contamination. The effectiveness of these measures should be demonstrated.

There should be adequate facilities for the testing of raw materials, packaging components, intermediates and finished food additives and GRAS substances.

5.3.2 Equipment

Equipment used in the production, processing, packaging, testing or storage of a food additive or GRAS substance shall be maintained in a good state of repair and should be of suitable size, construction and location to facilitate cleaning, maintenance and correct operation, depending on the type of processing (e.g., batch *versus* continuous) (See also 21 CFR 117.40).

Equipment should be commissioned and/or inspected before use to ensure that it is functioning as intended.

Where equipment is located outdoors there should be suitable control to minimize the risk to food additive and GRAS substance safety and quality from the environment (e.g., processing within a closed system).

5.3.2.1 Equipment Construction

Process equipment must be constructed so that contact surfaces do not contaminate or otherwise alter the quality of the food additive or GRAS substance. Substances required for operation, such as lubricants or coolants, should generally not come into contact with raw materials, packaging materials, intermediates or finished food additives and GRAS substances. Where contact is possible, substances suitable for use in food applications should be utilized.

Equipment should be designed to minimize the possibility of contamination caused by direct operator contact in such activities as the unloading of centrifuge bags, use of transfer hoses (particularly those used to transfer powders) and the operation of drying equipment and pumps. The sanitary design of transfer and processing equipment should be evaluated and managed in a manner to minimize potential contamination of the product (e.g., installation of backflow preventers, management of cross contamination, etc.). Equipment with moving parts should be assessed with regard to the integrity of seals and packing materials to control the risk of contamination.

5.3.2.2 Equipment Maintenance

Documented procedures should be established and followed for inspection and maintenance of critical equipment used in the production, processing, packaging, testing and/or holding of the food additive or GRAS substance. Records should be maintained of the use and maintenance of quality-critical equipment. These records can be in the form of a log, computer database or other appropriate documentation.

Repairs shall be accomplished in a manner that protect the safety and quality of the product. Repairs should be documented for quality-critical equipment.

5.3.2.3 Computer Systems

Computer systems that may impact food additive or GRAS substance quality should have sufficient controls for operation, maintenance and prevention of unauthorized access or changes to computer software, hardware or data, including:

- Procedures for checking the equipment at appropriate intervals;
- Establishment of appropriate cyber security measures to prevent unauthorized access;
- Retention of suitable back-up or archival systems such as copies of the program and files; and
- Assurance that changes are verified, documented, and only made by authorized personnel.

5.3.3 Utilities

Utilities (e.g., nitrogen, compressed air, steam, etc.) used in the production, storage or transfer of materials that could impact food additive or GRAS substance quality should be assessed and appropriate action taken to control the risk of contamination and cross-contamination.

5.3.4 Water

Water and water systems used in the manufacture of food additives and GRAS substances should be demonstrated to be of suitable quality for their intended use. Unless otherwise justified, process water supply shall be sufficient for the operations intended and shall be derived from an adequate source, such as U.S. Environmental Protection Agency[7] or World Health Organization[8] guidelines for drinking (potable) water quality.

If drinking (potable) water is insufficient to assure quality or higher chemical and/or microbiological water quality specifications are required, appropriate controls and specifications should be set.

Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be specified and monitored with appropriate action limits.

5.4 Work Environment

Where the food additive or GRAS substance is exposed to the environment during manufacture it should be in an appropriate environment to minimize contamination. The manufacturer should apply suitable controls to maintain that environment (per 21 CFR 117.35).

5.4.1 Air Handling

Where an air handling system is installed to provide protection to the food additive or GRAS substance, the food additive and GRAS substance manufacturer should demonstrate its conformance to specifications for intended use.

5.4.2 Controlled Environment

A controlled environment may be necessary to avoid exposure to environmental factors, such as moisture, heat, air or light. The degree of protection required should be appropriate to the product and process as determined by the additive and GRAS substance manufacturer. Food additive and GRAS substance production unit air handling systems should be designed to prevent cross-contamination. For dedicated areas processing the same food additive or GRAS substance, it may be permissible to recycle a portion of the exhaust air back into the same area. The adequacy of such a system for multi-use areas, especially if several products are processed simultaneously, should be assessed for potential cross-contamination.

Special environments required by some processes should be monitored to assure product quality (e.g., inert atmosphere or protection from light). If interruptions in the special environment occur, adequate evidence and appropriate rationale should be documented to show that such interruptions have not compromised the quality or safety of the food additive or GRAS substance.

5.4.3 Cleaning and Sanitary Conditions

Adequate cleanliness is an important consideration in the design and management of food additive and GRAS substance manufacturing facilities. Buildings used in the production, processing, packaging or holding of food additives and GRAS substances must be maintained in an appropriately clean and sanitary condition according to the type of processing conducted (e.g., open/closed systems).

Where maintenance of clean and sanitary conditions is critical to food additive and GRAS substance quality, documented procedures should assign responsibility for cleaning and, where appropriate, sanitation. Such written procedures should describe in sufficient detail the cleaning schedules, methods, equipment and materials to be used in cleaning the buildings and facilities. These cleaning procedures should be demonstrated to be effective, followed and documented.

Certain food additive and GRAS substance processes may not require sanitization of equipment (i.e., use of sanitizing processes or chemicals) to provide adequate cleaning and protection against microorganisms. In such cases, cleaning processes suitable to ensure the safety and quality of the food additive or GRAS substance should be developed and documented. For complete definitions of the above terms (e.g., sanitization), see Appendix A.

5.4.4 Pest Control

The food additive and GRAS substance manufacturer should have a documented pest management program consistent with the plant's food safety plan. Effective measures shall be taken to exclude pests from the manufacturing areas and to protect against the contamination of food additives and GRAS substances on the premises by pests. However, any pesticides used in the plant must be used in a manner that prevents cross contamination.

5.4.5 Lighting

Adequate lighting must be provided to facilitate cleaning, maintenance and proper operations. Lighting must be designed in a manner to minimize possible contamination of the product (e.g., shatter proof or shielding) to prevent any lighting component from falling into the product (per 21 CFR 117.20(b)).

5.4.6 Sewage and Refuse

Sewage, refuse and other waste in and from the building and immediate surrounding area should be segregated and disposed of in a safe, timely and sanitary manner. If waste is not disposed of in a timely manner, it shall be suitably identified and stored in an appropriate manner. Containers and/or pipes for waste material should be clearly identified.

Traffic patterns should be evaluated to minimize potential contamination from refuse removal.

5.4.7 Washing and Toilet Facilities

Adequate personnel washing facilities must be provided; these should include hot and cold water, soap or detergent, air dryers or single service towels and clean toilet facilities separate from but easily accessible to working areas. Adequate facilities for handwashing, showering and/or changing clothes should be provided, where appropriate. Handwashing stations should also be provided throughout the production area as appropriate.

6. OPERATIONS

6.1 Planning of Operations

The food additive and/or GRAS substance manufacturer should plan and develop the processes and controls needed for safe product manufacture.

These plans and controls should be appropriate to the production process, food additive and GRAS substance specifications, equipment and facilities used in the manufacture of the product.

Key aspects of the planning of a suitable process and its controls are identified in Section 4.4.4.2.

Planning of operations also includes:

- Environmental and hygiene control programs to minimize contamination;
- Supply chain management program;
- Allergen control program(s), if appropriate; and
- Documented testing programs for quality-critical materials, including food additives and GRAS substances, which include appropriate specifications, sampling plans, and test and release procedures.

6.2 Customer-Related Processes

6.2.1 Determination of Requirements Related to the Product

The food additive and GRAS substance manufacturer should address the food additive and GRAS substance quality, labeling and delivery requirements of the customer. Additional requirements, whether customer-specific, legal or regulatory (e.g., compendial material and general monographs), should be agreed by both parties. Requirements not stated by the customer but necessary for specified or intended use, where known, should be considered.

6.2.2 Review of Requirements Related to the Product

The food additive and GRAS substance manufacturer and customer should mutually agree upon the requirements identified in 6.2.1 before supply commences. The manufacturer should have the facility and process capability to meet the mutually agreed specifications consistently. Where the requirements determined in Section 6.2.1 are changed, this review should be repeated before supply recommences.

6.2.3 Customer Communication

There should be provisions for providing accurate and pertinent communication to the customer. Provisions should be made for replying to customer inquiries, contracts and order handling requirements. A procedure should also be in place to document and respond appropriately to customer feedback and complaints.

6.3 Design and Development

The ISO-9001 Standard includes requirements for ensuring control over design and development activities. Companies involved in such activities are recommended to follow the requirements of ISO-9001. FSMA (21 CFR Part 117) also includes GMP requirements for firms manufacturing products in the U.S. or for the U.S. market.

Full GMP is not always applicable during the design and development of new food additives and GRAS substances. However, development batches of food additives and GRAS substances that are intended for use in food products should be manufactured in accordance with the applicable provisions of this Guide.

6.4 Purchasing

Food additive and GRAS substance manufacturers should establish a written supply-chain program (per 21 CFR Part 117 Subpart G). It is an IFAC best practice that a written supply chain program includes a supplier risk assessment, which should be risk-based, recorded in writing and documented when completed. Under FSMA, the receiving facility must establish and implement a risk-based supply-chain program for those raw materials and other ingredients that require a supply-chain-applied control due to their potential association with a hazard.

If no hazards are identified or a hazard will be controlled by the receiving facility, there will be no impact on the supplier. If a preventive control is applied by the supplier, the receiving facility must verify the supply-chain-applied control by onsite audits, sampling and testing, records review, or other appropriate supplier verification activities, or by obtaining documentation and documenting that review and assessment.

6.4.1 Purchasing Process

Food additive and GRAS substance manufacturers should have a system for selecting and approving suppliers of quality-critical materials and services (e.g., subcontract manufacturers and laboratories). As an IFAC best practice, food additive and GRAS substance manufacturers should implement supplier qualification programs (i.e., for raw materials used in the production of food additives and GRAS substances) and will be subject to supplier qualification as the supplier of food additives and GRAS substances that will be used in food products.

Supplier approval by a quality function independent from purchasing should require an evaluation of the supplier's quality management system, including adequate evidence that they can consistently meet agreed requirements. As required by FSMA, the following components must also be included as part of the supply-chain management system:

- Determining appropriate supplier verification activities (including determining the frequency of conducting the activity) (as required by 21 CFR117.425);
- Conducting supplier verification activities (as required by 21 CFR 117.430 and 117.435); and
- Written documentation of supplier verification activities (as required by 21 CFR 117.475).

After the initial audit of the supplier's facility, there should be periodic audits of the supplier's manufacturing facility thereafter. Records of these activities should be maintained. Requirements applicable to onsite audits are delineated in 21 CFR 117.435.

Materials should only be purchased against an agreed specification from approved suppliers.

6.4.2 Purchasing Information

Purchasing agreements should describe the material or service ordered including, where critical to food additive and GRAS substance quality or safety, the following:

- The name, type, class, style, grade, item code number or other precise identification traceable to the raw material and packaging specifications;
- Drawings, process requirements, inspection instructions and other relevant technical data, including requirements for approval or qualification of supplier product, procedures, process equipment and personnel;
- Adherence to the appropriate sections of this Guide for relevant contract manufacturers or laboratories; and
- A statement to notify the food additive and GRAS substance manufacturer of significant changes in quality-critical raw materials.

6.4.3 Supplier Qualification and Periodic Verification

The breadth of raw materials used to produce a particular food additive or GRAS substance can range from mined and agricultural materials to finished, synthetic substances. The food additive and GRAS substance manufacturer shall therefore conduct a hazard analysis on the grades and types of materials that are needed for the intended use in their manufacturing process.

The processes for conducting supplier qualification under FSMA are described in 6.4.1 as well as 21 CFR Part 117.

The supplier and quality-critical material qualification system should include evaluation criteria. This information may include, but is not limited to:

- Applicable material, technical, and/or regulatory information;
- Supplier and manufacturing process information (including identification of the original manufacturing site);
- Verification that the material was manufactured using appropriate quality and safety standards and/or GMPs, as applicable;
- Composition and impurity information, as applicable;
- Supply chain and security information;
- Specifications; and
- Stability or shelf life information.

When conducting supplier verification activities for raw materials and other ingredients, companies should consider the following additional activities, as appropriate:

- Audits conducted by the supplier or a third-party;
- Sampling and testing of the raw material or other ingredient;
- Review of the supplier's relevant food safety records; and
- Other appropriate supplier verification activities based on supplier performance and the risk associated with the raw material or other ingredient.

For quality-critical materials, a site audit of the supplier is recommended either by the food additive and GRAS substance manufacturer or by a qualified third party audit provider (FSMA specifies the conditions for which a qualified third-party may be used in 21 CFR 117.3, 117.180(b) and 117.435). The receiving facility should not rely on a supplier’s self-affirmation. Questionnaires should not be used as a substitute

for on-site assessment unless the risk assessment adequately demonstrates why a questionnaire is adequate.

A supplier's qualification status should be periodically reevaluated to provide assurance of on-going compliance to the food additive and GRAS substance manufacturer's requirements. The frequency of audits and/or reevaluation should be based on a documented risk-based assessment; however, a defined period should be established where re-verification is required since changes may occur in a supplier's control program over time. Suppliers found not to be suitable should either be removed from this list or an appropriate corrective action plan should be developed with the supplier.

FSMA prescribes a variety of required supplier verification activities which are outlined in the Preventive Controls rule. Manufacturers should refer to 21 CFR Part 117 Subpart G when establishing supplier qualification programs and designing record keeping programs to ensure compliance with FSMA.

Per 21 CFR 117.430(c)(2), written assurance must be provided from suppliers meeting the definition of a "qualified facility" (essentially a "very small business") that the supplier is producing the raw material or other ingredient in compliance with applicable U.S. FDA food safety regulations (or, when applicable, relevant laws and regulations of a country whose food safety system FDA has officially recognized as comparable or has determined to be equivalent to that of the U.S.). The written assurance must include either:

- A brief description of the preventive controls that the supplier is implementing to control the applicable hazard in the food; or
- A statement that the facility is in compliance with State, local, county, tribal, or other applicable non-Federal food safety law, including relevant laws and regulations of foreign countries.

6.4.4 Verification of Purchased Product

There should be procedures for the approval and release of quality-critical material.

Upon receipt, quality-critical materials should be segregated from materials that have been accepted and should not be used prior to acceptance. Effective segregation can be established with suitable identifying labels, signs and/or other manual documentation systems. When segregation and stock control are managed with computer systems in lieu of a physical stock control, then system controls should prevent the use of unreleased material.

Segregation may not be feasible for materials supplied via pipelines. In these cases the food additive and GRAS substance manufacturer should establish an agreement with the supplier so that the manufacturer is notified of material that does not meet specification.

Sampling activities should be conducted under defined conditions, in accordance with a defined sampling method and using procedures designed to prevent contamination and cross-contamination. Sampling may also be used and documented as a verification measure of any supplier imposed hazard controls, and may need to be considered in supplier qualification programs.

Quality-critical materials used in the manufacture of a food additive and GRAS substance should be tested or otherwise verified prior to use. Verification should include a check of the supplier certificate of analysis (COA) and other assessments, as appropriate (e.g., checking batch numbers, verifying that the COA received matches the COA generated by the manufacturer).

Bulk deliveries should have additional controls to assure material purity and freedom from contamination (e.g., dedicated tankers, tamper-evident seals, a certificate of cleaning, analytical testing and/or audit of the supplier).

These procedures, activities and results should be documented and retained.

6.5 Production and Service Provision

6.5.1 Control of Production and Service Provision

Production activities should be carried out under controlled conditions (see also Section 5.4.2).

Specific examples of important controls, some of which may not be applicable to all food additive and GRAS substance manufacturers, are illustrated in the following sections.

6.5.1.1 Production Instructions and Records

As an IFAC best practice, production instructions and records are always expected, but may differ for the type of operation (e.g., batch *versus* continuous processes).

There should be a controlled document that describes how the food additive and GRAS substance is produced (e.g., master production instructions, master production and control records, process definitions, etc.).

For batch processes, an accurate reproduction of the appropriate master production instructions should be issued to the production area. For continuous processes, a current processing log should be available.

Records should be available for each batch of food additive or GRAS substance produced and should include complete information relating to the production and control of each batch. For continuous processes the batch and its records should be defined (e.g., based on time or defined quantity). Records may be in different locations but should be readily retrievable.

Records for both batch and continuous processing, where critical to food additive and GRAS substance quality, must be kept as original records, true copies or electronic records, and typically include:

- Date/time each step was completed or date/time log of key parameters (per 21 CFR 117.305(b) and 21 CFR 117.305(f)(s)), key parameters may include actual values and observations obtained during monitoring and, as appropriate, during verification activities);

- Identification of persons performing, directly supervising or checking each significant step, operation or control parameter;
- Identification of major equipment;
- Raw material traceability (e.g., batch number and quantities of raw material/intermediate);
- In-process and laboratory control results;
- The quantity produced for the defined batch unless not quantifiable (e.g., as in some continuous processes);
- Verification of the packaging and labeling should be appropriately controlled;
- Indication of package size of food additive and GRAS substance product containers;
- Results of final product inspection and disposition; and
- The signature or initials of the person performing the activity.

All records collected must be accurate, indelible, and legible, created concurrently with performance of the activity documented. All records should be as detailed as necessary to provide history of work performed.

6.5.1.2 Equipment Cleaning

Cleaning and sanitization, where appropriate, procedures should be justified and their effectiveness documented. Cleaning plans should contain sufficient detail to allow operators to clean each type of equipment in a reproducible and effective manner. Records confirming that these procedures have been followed must be generated after each cleaning and retained including the signature or initials of the person performing the clean.

Any cleaning compounds and sanitizing agents used in cleaning and sanitizing procedures shall be safe and adequate for the products intended use. Compliance with this requirement must be verified by any effective means, including purchase of these substances under a letter of guarantee or certification or examination of these substances for contamination.

Only the following toxic substances used in sanitation may be used or stored in a plant where food is processed or exposed (as specified by 21 CFR 117.35(b)):

- Those required to maintain clean and sanitary conditions;
- Those necessary for use in laboratory testing procedures;
- Those necessary for plant and equipment maintenance and operation; and
- Those necessary for use in the plant's operations.

Equipment and utensils should be cleaned and sanitized where critical to food additive or GRAS substance quality. All food contact surfaces shall be cleaned as frequently as necessary to protect against allergen cross-contact and against contamination of food (per 21 CFR 117.35(d)). Non-food-contact surfaces of equipment must be cleaned in a manner and as frequently as necessary to protect against allergen cross-contact and against contamination (as required by 21 CFR 117.35(e)).

Where multi-purpose equipment is in use it is important to be able to determine previous usage when investigating cross-contamination or the possibility of such contamination. Records should be maintained and processes implemented that are sufficient to minimize the potential for allergen cross-contact and against contamination.

For continuous processing the frequency of equipment cleaning should be determined by the manufacturer, documented with justification.

6.5.1.3 Recovery of Solvents, Mother Liquors and Second Crop Crystallizations

Where solvents are recovered and reused in the same process or different processes they should meet appropriate standards prior to reuse or mixing with other approved material.

Mother liquors or filtrates containing recoverable amounts of food additives and GRAS substances, reactants or intermediates are frequently reused. Such processes should be documented in the production records or logs to enable traceability.

6.5.1.4 In-Process Blending or Mixing

In-process blending or mixing to assure batch uniformity or to facilitate processing should be controlled and documented. If the intent of the operation is to ensure batch uniformity it should be performed so as to assure homogenous mixing of materials to the extent feasible and should be reproducible from batch to batch.

The blending process should be documented in a manner that allows traceability to the individual inputs that make up the blend.

6.5.1.5 In-Process Control

In-process inspection and testing should be performed based upon monitoring the process or actual sample analysis at defined locations and times. Sampling methods should be documented to ensure that the sample is representative and clearly labeled.

Any sampling or other in-process controls must be handled in a manner that protects against allergen cross-contact, contamination and growth of undesirable microorganisms. In-process samples should not be returned to production for incorporation into the final batch.

The results of in-process tests should be recorded and should conform to established process parameters or acceptable tolerances. Work instructions should define the procedure to follow and how to utilize the inspection and test data to control the process. In those situations where in-process testing is performed by the production department and where approval to continue with the process is issued within the production department, the specified tests should be performed by trained personnel and the results recorded.

6.5.1.6 Records of Equipment Use

Records of quality-critical equipment use should be retained. These records should indicate the sequence of cleaning, maintenance, calibration and production activities as applicable. Records should be retained in accordance with Section 6.5.1.1 of this Guide and other Preventive Control recordkeeping requirements if applicable. Records should be available and consulted during verification activities, as appropriate.

6.5.1.7 Packaging

Packaging materials should be designed and selected to be safe and suitable for contact with the food additive and GRAS substance. Hazard analysis must include consideration of hazards that may be introduced during packaging and/or labeling activities (e.g., allergen cross-contact or contamination of packaging materials with microorganisms or foreign substances) (21 CFR 117.130). Procedures should be employed to protect the quality and purity of the food additive or GRAS substance during packaging activities.

Procedures should be implemented to verify that the correct labels are printed and issued and that the labels contain the correct information. Packaging and labeling operations should be designed to prevent mix-ups. Packaging and labeling facilities should be inspected immediately before use to ensure that materials that are not required for the next packaging operation have been removed.

6.5.1.7.1 Packaging Systems

A food additive or GRAS substance packaging system should include the following features, where appropriate:

- Documented specifications and examination or testing methods;
- Cleaning procedures where containers are reused;
- Containers that are made from materials approved for use in food;[8]
- Containers that provide adequate protection against deterioration or contamination of the food additive or GRAS substance during transportation and recommended storage;
- Containers that do not interact with or contaminate the food additive or GRAS substance; and
- Storage and handling procedures which protect containers and closures and minimize the risk of contamination, damage or deterioration and which will avoid mix-ups (e.g., between containers that have different specifications but are similar in appearance).

Additionally, tamper-evident seals should be considered when appropriate.

If food additive or GRAS substance containers are re-used, previous labeling should be completely removed or defaced. Hazard analysis for re-used containers and packages should include consideration of cross-

contact, allergen control, and contamination with microorganisms or foreign materials.

6.5.2 Verification of Processes for Production and Service Provision

An important factor in the assurance of product quality includes the adequate verification that preventive controls are implemented and effective. Each step of the manufacturing process should be controlled to the extent necessary to ensure that the food additive or GRAS substance meets established specifications and is safe for its intended use. The concept of process verification is a key element in ensuring that these quality assurance goals are met. The process reactions, operating parameters, purification steps, impurities and key tests needed for process control should be documented, thus providing the basis for verification.

6.5.3 Identification and Traceability

6.5.3.1 Traceability

Quality-critical items (e.g., raw materials, packaging materials, intermediates and finished food additives and GRAS substances) must be clearly identified and traceable through records. These records should allow traceability of the food additive or GRAS substance both upstream and downstream, and must provide details about the product and facility from which the product was initially received as well as information about the product's destination, such as the date it is to be released and the location of receiving firm (as required by 21 CFR 1.337 and 21 CFR 1.345). Identification of quality-critical items used in batch production processes should be traceable through the batch numbering system or other appropriate system. Identification of raw materials used in food additives and GRAS substances produced by continuous processing should indicate the timeframe during which a particular batch of raw material was processed through the plant.

Raw materials are sometimes stored in bulk tanks or other large containers, making precise separation of batches difficult. Nevertheless, the use of such materials should be documented in production records.

Written procedure must be established for traceability, which include monitoring and corrective action if traceability fails. Traceability plans must also be considered when establishing the recall plan for the facility. Traceability systems should be periodically challenged to verify effectiveness (e.g., mock recall exercises).

6.5.3.2 Inspection and Test Status

There should be a system to identify the inspection status of quality-critical items including raw materials, packaging materials, intermediates and finished food additives and GRAS substances. Materials on hold for inspection prior to release or for non-conformities should have a means of identification. Continuously-fed materials may need special consideration in order to satisfy these requirements.

6.5.3.3 Labeling

Labeling for food additive and GRAS substance packages is subject to national and international regulatory requirements, which may include transportation and safety measures. At a minimum, labels should include:

- The name of the food additive or GRAS substance and grade if applicable;
- The manufacturer's and/or distributor's name;
- The batch number from which the complete batch history can be determined; and
- Special storage conditions, if applicable.

6.5.4 Preservation of Product

6.5.4.1 Handling, Storage and Preservation

Hazard analysis should include consideration of hazards that may be introduced during handling or storage. Food additives, GRAS substances, intermediates and raw materials should be handled and stored under appropriate conditions of temperature, humidity and light so that their identity, quality and purity are not affected. There should be means to monitor and control temperature for materials that require controlled temperatures to ensure the safety and integrity of the product, such as frozen items, during storage or transport.

Storage must minimize the potential for any cross-contamination or allergen cross-contact (21 CFR 117.93). Adequate space should be provided for storage of materials as is necessary for maintenance, sanitary operations and the production of safe food. In most cases, outdoor storage of raw materials (e.g., acids, other corrosive substances or explosive materials), food additives or GRAS substances is acceptable provided the containers give suitable protection against deterioration or contamination of their contents, identifying labels remain legible and containers are adequately cleaned prior to opening and use.

Records of storage conditions should be maintained if they are critical for the continuing conformance of the material to specification.

6.5.4.2 Delivery and Distribution

Distribution records of food additive and GRAS substance shipments must be kept. These records should identify, by batch, where and to whom the food additive or GRAS substance was shipped, the amount shipped and the date of shipment so as to facilitate retrieval if necessary. Where food additives or GRAS substances are handled by a series of different distributors, it should be possible to trace them back to the original manufacturer and not just to the previous supplier.

Food additive and GRAS substances should only be supplied within their recommended shelf life.

Food additives and GRAS substances must be transported under appropriate conditions to maintain food safety. Vehicles and transportation equipment should be designed to allow for adequate cleaning and be

capable of maintaining labeled storage conditions, such as proper temperature controls. Controls should also be in place to prevent contamination of food additives and GRAS substances during transportation such as contact with allergens, non-food items, or microbiological hazards present in the same containers. Controls should also address residues and carry over from previous loads.

Food additive and GRAS substance manufacturers transporting their products in the U.S. should consult the FSMA Final Rule on Sanitary Transportation of Human and Animal Food (see 21 CFR Part 1 Subpart O). In general, these regulations are applicable to perishable products or products that are exposed to the environment during shipping. However, food additive and GRAS substance manufacturers shipping their products in the U.S. should consult the regulations to determine applicability.

6.6 Control of Measuring and Monitoring Devices

Process monitoring and verification instruments, including computerized systems, should be calibrated, checked for accuracy and maintained, and calibration is required. This includes in-process instruments as well as test equipment used in the laboratory. The control program should include the standardization or calibration of instruments and equipment at suitable intervals in accordance with an established documented program. This program should contain specific directions, schedules, limits for accuracy and precision. Calibration standards should be traceable to recognized national or compendial standards as appropriate. The current calibration status of quality-critical equipment should be known, documented and verifiable to users.

Corrective action plans should be established for calibration failures. Instruments and equipment not meeting established specifications should not be used and an investigation should be conducted to determine the validity of the previous results since the last successful calibration.

Records of all calibration and maintenance activities should be retained and included, where appropriate, in food safety plans and/or preventive controls plans.

7. Performance Evaluation

7.1 General

The organization should plan and implement the monitoring, measurement and improvement activities required to demonstrate conformity of the food additive and GRAS substance to customer requirements and to ensure conformity of the quality management system to this Guide.

The organization should evaluate opportunities for improvements through the measurement and analysis of product and process trends.

7.2 Monitoring and Measurement

7.2.1 Customer Satisfaction

The manufacturer should establish activities to assess customer satisfaction. Such activities can include customer complaints, return of food additives or GRAS

substances and customer feedback. This information should drive activities that strive to continuously improve customer satisfaction.

7.2.2 Internal Audit

The food additive and GRAS substance manufacturer should carry out a comprehensive system of planned and documented internal quality audits. These audits should determine whether the quality activities comply with the quality management system and are effective in protecting food safety.

The scope and the frequency of the audits should be defined on the basis of the importance of the intended use of the food additive or GRAS substance to ensure GMP compliance and food safety. The key stages of a production process should be examined to determine whether the manufacturer adequately controls these steps so the process performs consistently. Overall, an audit should assess the food additive and GRAS substance manufacturer's capability to deliver a product that consistently meets established specifications in an environment that ensures the safety of the food additive or GRAS substance.

The audit team should consist of trained personnel as appropriate to the scope and purpose of the audit. The internal audit should examine all systems defined in this Guide; however, not all systems need to be reviewed during each internal audit. The frequency of review should be defined and documented.

7.2.3 Monitoring and Measurement of Processes

The food additive and GRAS substance manufacturer should identify the tests and measurements necessary to adequately control manufacturing and quality management system processes to ensure food safety. Where critical to food additive and GRAS substance quality or safety, techniques that are used to verify that the processes and hazards identified in the preventive controls program are under control should be established.

Corrective action should be taken to ensure the food additive or GRAS substance meets requirements when deviations from planned results occur.

Periodic reviews of key indicators such as process quality attributes and process failures should be conducted to assess the need for improvements.

7.2.4 Monitoring and Measurement of Product

The food additive and GRAS substance manufacturer should establish the test methods and procedures to ensure the product consistently meets specifications.

Analytical methods should be fit for purpose. The analytical methods may be those included in the current edition of the appropriate compendium. However, the methods may also be non-compendial or another accepted standard.

If the food additive and/or GRAS substance manufacturer claims that their product is in compliance with a compendium monograph, then:

- Non-compendial analytical tests should be demonstrated to be equivalent to those in the compendia; and
- The product should comply with applicable compendium general chapters and notices.

7.2.4.1 Laboratory Controls

Laboratory controls should include complete data derived from tests necessary to ensure conformance with specifications and standards including:

- A description of the sample received for testing together with the material name, batch number or other distinctive code and date the sample was taken;
- A statement or SOP referencing each test method used;
- A record of raw data secured during each test including graphs, chromatograms, charts and spectra from laboratory instrumentation, identified to show the specific material and batch tested;
- A record of calculations performed in connection with the test;
- Test results and how they compare with established specifications; and
- A record of the person who performed each test and the date(s) the tests were performed.

There should be a documented procedure for the preparation of laboratory reagents and solutions. Purchased reagents and solutions should be labeled with the proper name, concentration and expiry date. Records should be maintained for the preparation of solutions, including the name of the solution, date of preparation and quantities of material used. Volumetric solutions should be standardized according to an internal method or by using a recognized standard. Records of the standardization should be maintained.

Where used, primary reference reagents and standards should be appropriately stored and need not be tested upon receipt provided that a COA from the supplier is available. Secondary reference standards should be appropriately prepared, identified, tested, approved and stored. There should be a documented procedure for the qualification of secondary reference standards against primary reference standards. The re-evaluation period should be defined for secondary reference standards and each batch should be periodically re-qualified in accordance with a documented protocol or procedure.

7.2.4.2 Finished Product Testing and Release

Finished food additive and GRAS substance testing should be performed on each batch to ensure that the food additive or GRAS substance conforms to documented specifications. There should be a procedure to ensure that appropriate manufacturing documentation, in addition to the test results, is evaluated prior to release of the finished food additive or GRAS substance. The quality unit should be responsible for the release of the finished food additive or GRAS substance.

For food additives and GRAS substances produced by continuous processes, assurance that the food additive or GRAS substance conforms to documented specifications may be achieved through the results of in-process testing or other process control records.

7.2.4.3 Out-of-Specification Test Results

Out-of-specification (OOS) test results should be investigated and documented according to a documented procedure.

Retest sample results may only be used to replace the original test result if it is demonstrated that the original result is erroneous based on a documented investigation.

When statistical analysis is used, both the original and retest data must be included. The OOS procedure should define which statistical techniques are to be used and under what circumstances.

These same principles apply when the sample is suspected of not being representative of the material from which it was taken.

7.2.4.4 Retained Samples

Where practical, a representative sample of each batch of the food additive or GRAS substance should be retained. The retention period should be appropriate to the expiration or re-evaluation date. (See Glossary for definition of terms.) The retained samples should be stored and maintained in such a manner that they are readily retrievable in facilities that provide a suitable environment. The sample size should be at least twice the amount required to perform complete specification testing.

7.2.4.5 Certificates of Analysis

The organization should provide certificates of analysis (COAs) to the required specifications for each batch of food additive or GRAS substance.

COAs should contain a minimum of the following information:

- Identity of the food additive or GRAS substance, including the compendium, trade name, the grade of the material and other applicable designations;
- Manufacturer and the site of manufacture including address and telephone number;
- Lot/Batch number;
- Date of manufacture;
- Date of re-evaluation /expiration date depending on stability of the material;
- Descriptors of test parameters, acceptance criteria, and test results. Listing of tests performed, including:
    - name of the test;
    - test method reference;
    - actual testing results; and
    - acceptance criteria or a reference to the acceptance criteria (if reduced frequency testing is justified, then the test result guaranteed by reduced testing should be clearly identified with an appropriate notation);
- Identity of the authorized individual responsible for approval; and
- Date the COA was issued.

7.2.4.6 Impurities

Where possible, food additive and GRAS substance manufacturers should identify and set appropriate limits for impurities. The limits should be based upon appropriate safety data, as described in official compendia or other requirements. Manufacturing processes should be adequately controlled so that the impurities do not exceed such established limits.

Some food additives and GRAS substances are extracted from or purified using organic solvents. These solvents are normally removed by drying. Final product must meet compendial regulatory or manufacturer specifications for solvent residues.

While compendial monographs (e.g., FCC) play an important role in establishing GMPs, no compendial monograph can provide limits and tests for all possible impurities. Therefore, it is the responsibility of the food additive and GRAS substance manufacturer to ensure they understand their manufacturing process well enough so they can evaluate the presence of new or additional impurities pertinent to their product(s).

7.2.4.7 Stability

The quality of food additives and GRAS substances is an important factor contributing to the overall quality of the food products in which they are used. It is important to understand the stability of food additives and GRAS substances under appropriate conditions of packaging, storage, and use, so that adherence to quality specifications can be assured at the time of use of these food additives and GRAS substances.

While many food additives and GRAS substances are stable and may not require extensive testing to assure stability, the stability of food additives and GRAS substances is an important factor contributing to the overall quality of the food product. Generally, stability testing should be performed for any substance with validated shelf-life running from six months to three years. Historical data that is statistically significant can be used to validate shelf-life.

Where historical data does not exist, a documented testing and/or evaluation program designed to assess the stability characteristics of the food additive or GRAS substance should be undertaken. The results of such stability testing and/or evaluation may be used in determining appropriate storage conditions and retest or expiry dates. The testing program should include the following, as appropriate:

- The number of batches, test sample sizes and testing intervals;
- Storage conditions for stability samples retained for testing;
- Suitable stability-indicating test methods; and
- Containers demonstrated to simulate the market container used for the stability samples, where possible.

Some food additives and GRAS substances may be available in different grades (e.g., various molecular weights of a polymer or different monomer ratios, different particle sizes, bulk densities, etc.) or may be mixtures of other food additives and GRAS substances. These food additives and

GRAS substances may be very similar to others within a product group. Minor quantitative differences of some of the components may be the only significant variation from one product to another. For these types of food additives and GRAS substances, a "model product" approach may be appropriate to assess the stability of similar food additives and GRAS substances.

Stability studies of this type may involve selection of several "model products" that would be expected to simulate the stability of the product group being assessed. A selection of a model product should be scientifically sound and documented. Data from stability studies of such "model products" can be used to determine estimated stability for similar food additives and GRAS substances.

The stability of food additives and GRAS substances varies. For the purpose of this Guide, they have been put into three categories. These are only recommendations and the suggestions under these categories should be customized to best address material stability.

Materials with Shelf Life > 36 Months
Food additives and GRAS substances with shelf life greater than 36 months typically have the following attributes:

- The demonstrated history of stability that deems them adequately stable in the specified packaging for greater than 36 months and may be limited only due to the durability of the packaging or labeling;
- Stability can be predicted based on their known attributes; and
- Stability is not expected to be altered by changes in the manufacturing process.

For food additives and GRAS substances that are classified here with sufficient literature citations or stability studies to show the food additive or GRAS substance remains unchanged for greater than 36 months, a further ongoing stability testing program is unnecessary. There should be a report, supported by internal studies and/or literature citations, to support the classification of the food additive or GRAS substance. A stability statement or reference to a stability test is all that is required to demonstrate stability to users. A summary report should be available to the user upon request.

Materials with Shelf life 12-36 Months
These food additives and GRAS substances typically have:

- A retest interval of les36 months but greater than or equal to 12 months;
- Stability indicating parameters; and
- Data to support the assigned re-evaluation interval or expiration date.

For food additives and GRAS substances that are classified here, there should be a report, supported by studies, to sustain the continuing classification of the food additive or GRAS substance. A stability statement or reference to a stability test is all that is required to

demonstrate stability to users. A summary report should be available to the user upon request.

Materials with Shelf life < 12 Months
These food additives and GRAS substances typically have:

- Re-evaluation intervals or expiration dates of less than 12 months; and/or
- Limited stability data to support the re-evaluation intervals or expiration dates.

For these food additives and GRAS substances, a stability reassessment program is strongly recommended. The testing program may be comprised of both long term and, where appropriate, accelerated storage conditions in packaging that properly simulates the packaging container/closure system.[9]

For new or novel chemical food additives and GRAS substances, the shelf life determination may change during the development program as stability data becomes available.

The primary purpose of a food additive or GRAS substance stability study is to provide evidence that the food additive or GRAS substance will continue to meet quality standards from the point at which manufacture has been completed (typically at the time of packaging) and up until the point at which the package is opened. Any stability issues subsequent to opening the package are the responsibility of the user.

Stability studies for bulk shipments (e.g. barges, railcars, road tankers, totes, etc.) pose particular challenges in the design of an appropriate stability study. However, extrapolation from data collected using the methods outlined above is possible where consideration is given to the risk factors for food additive or GRAS substance stability posed by these transportation and storage methods.

7.2.4.8 Shelf Life/Retest Periods

A shelf life expectation and/or retest period may be assigned to each food additive or GRAS substance and communicated to the customer.

7.3 Control of Nonconforming Product

Raw material, intermediate or finished food additives or GRAS substances found not to meet its specification should be clearly identified and controlled until a determination is made on the appropriateness of use. Incidences of non-conformance should be investigated to identify the cause. The investigation should be documented and appropriate action taken to prevent recurrence.

There should be a documented procedure defining how the retrieval of a raw material, intermediate, or finished food additive or GRAS substance from distribution should be conducted and recorded. In developing such procedures, manufacturers should refer to FDA guidelines and the requirements of the Reportable Food Registry.[10-11]

Procedures should exist for the evaluation and subsequent disposition of nonconforming products. Nonconforming product should be reviewed in accordance with documented procedures to determine if it may be:

- Reprocessed/reworked to meet the specified requirements;
- Accepted by the customer with their agreement;
- Re-graded for other applications; and/or
- Destroyed.

7.3.1 Reprocessing

Repetition of an activity that is a normal part of the manufacturing process (i.e., reprocessing) should only occur when it has already been documented that the food additive or GRAS substance may be made in that manner. In all other cases, the guidelines for reworking should be followed.

7.3.2 Reworking

An activity that is not a normal part of the manufacturing process (i.e., reworking) should only be conducted following a documented review of risk to food additive or GRAS substance/intermediate safety and quality and approval by the quality unit. As appropriate, when performing the risk assessment, consideration should be given to:

- Rework material meeting established specifications and characteristics;
- New impurities that may be introduced as a result of reworking;
- Potential for allergen cross-contact risk;
- Additional testing to control the reworking;
- Records and traceability to the original batches;
- Suitable acceptance criteria for the reworked material;
- Impact on stability or shelf life determination; and
- Performance of reworked material.

Batches of food additives or GRAS substances that do not conform to specifications individually must not be blended with other batches that do conform in an attempt to hide materials that are adulterated or are otherwise unfit for consumption.

7.3.3 Returned Food Additives and GRAS Substances

Returned food additives and GRAS substances should be identified and quarantined until the quality unit has completed an evaluation of their quality and suitability for resale. There should be procedures for holding, testing, reprocessing or reworking of the returned food additives and GRAS substances. Records for returned products should be maintained and should include the name of the food additive or GRAS substance and the batch number, reason for the return, quantity returned and ultimate disposition of the returned food additive or GRAS substance.

7.4 Analysis of Data

The food additive and GRAS substance manufacturer should develop methods for evaluating the effectiveness of its quality management and food safety systems. Such data can be derived from customer complaints, product reviews, process capability studies, internal and customer audits. A periodic management review of key indicators, such as product quality attributes, customer complaints and product nonconformities, may be conducted to assess the effectiveness of their quality program and identify areas for improvements.

7.5 Improvement

7.5.1 Continual Improvement

As an IFAC best practice, food additive and GRAS substance manufacturers should take proactive measures to improve safety, manufacturing and quality where appropriate to meet these GMP guidelines. The food additive and GRAS substance manufacturer should take proactive measures to improve manufacturing and quality management system processes. To identify opportunities for improvement, analysis of the following performance indicators may be considered:

- Causes of nonconforming product;
- Results of internal and external audits;
- Customer returns and complaints; and
- Process and operational failures.

7.5.2 Corrective Action

The food additive and GRAS substance owner, operator, or agent in charge of a manufacturing facility must establish, document and maintain procedures to ensure that if preventive controls are not properly implemented or found to be ineffective the following activities will take place to ensure food safety:

- Preventing all affected food additives and GRAS substances from entering into commerce if the food additive and GRAS substance owner, operator, or agent in charge of a manufacturing facility cannot ensure that it is not adulterated;
- Evaluating all affected food additives and GRAS substances for safety;
- Determining the root causes of nonconformities;
- Ensuring that corrective actions are implemented and effective to prevent recurrence; and
- Implementing and recording changes in procedures resulting from corrective action.

APPENDIX A DEFINITIONS AND GLOSSARY

As used throughout this Guide, the terms below have the following meaning. Wherever possible, definitions used by the International Conference on Harmonization have been used as the basis for this glossary. In some cases, terms have been used that are consistent with FSMA rules. If not defined below, please refer to definitions, which can be found in relevant parts of Section 21 in the Code of Federal Regulations.

Acceptance Criteria
Numerical limits, ranges or other suitable measures of acceptance for test results.

Batch (Lot)
A specific quantity of material produced in a process or series of processes so that it can be expected to be homogeneous. In the case of continuous processes, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch Number (Lot Number)
A unique combination of numbers, letters and/or symbols that identifies a batch and from which the production and distribution history can be determined.

Batch Process
A process that produces the food additive or GRAS substance from a discrete supply of raw materials that are present before the completion of the reaction.

Batch Record
Documentation that provides a history of the manufacture of a batch of food additive or GRAS substance.

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

Certificate of Analysis
A document listing the test methods, specification and results of testing a representative sample from the batch to be delivered.

Cleanliness
Keeping the food contact surfaces free of debris, dirt, and the like.

Contamination
The undesired introduction of impurities of a chemical or microbiological nature or foreign matter into or onto a raw material, intermediate or food additive or GRAS substance during production, sampling, packaging or repackaging, storage or transport.

Continuous Process
A process that continually produces material from a continuing supply of raw material

Critical
A process step, process condition, test requirement or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the food additive or GRAS substance meets its specification.

Cross-Contamination
Contamination of a material or product with another material or product.

Customer
The organization receiving the food additive or GRAS substance once it has left the control of the food additive and/or GRAS substance manufacturer; includes brokers, agents and users.

Deviation
Departure from an approved instruction or established standard.

Expiry (Expiration) Date
The date designating the time during which the food additive or GRAS substance is expected to remain within specifications and after which it should not be used.

Food Additive
A food additive is defined in Section 201(s) of the FD&C Act as any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use); if such substance is not GRAS or sanctioned prior to 1958 or otherwise excluded from the definition of food additives.

GRAS Substances
"GRAS" is an acronym for the phrase Generally Recognized As Safe. Under sections 201(s) and 409 of the FD&C Act, any substance that is intentionally added to food is a food additive, that is subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use, or unless the use of the substance is otherwise excluded from the definition of a food additive. GRAS substances are distinguished from food additives by the type of information that supports the GRAS determination, that it is publicly available and generally accepted by the scientific community, but should be the same quantity and quality of information that would support the safety of a food additive.

Intermediate
Material that must undergo further manufacturing steps before it becomes a food additive or GRAS substance.

Lot
See Batch.

Management
Person or group of people who direct and/or control an organization’s quality management system at the highest level. This can either be at the site or corporate level, depending on the way that the quality management system is organized.

Manufacture/Manufacturing Process
All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release and storage of food additives and GRAS substances and related controls.

Master Production Instruction (Master Production and Control Record)
Documentation that describes the manufacture of the food additive or GRAS substance from raw material to completion.

Material
A general term used to denote raw materials (starting materials, reagents and solvents), processing aids, intermediates, food additives or GRAS substances, packaging and labeling materials.

Model Product
A product that represents a group of similar products with respect to composition, functionality or specification.

Mother Liquor
The residual liquid that remains after crystallization or isolation processes.

Original Manufacturing Site
A location where a material is manufactured to the stage at which it is designated as a material for use in food additive or GRAS substance manufacturing.

Packaging Material
A material intended to protect an intermediate or food additive or GRAS substance during storage and transport.

Production
Operations involved in the preparation of a food additive or GRAS substance from receipt of materials through processing and packaging of the food additive or GRAS substance.

Quality Assurance
The sum total of the organized arrangements made with the object of ensuring all food additives and GRAS substances are of the quality required for their intended use and that quality systems are maintained.

Quality-Critical
Describes a material, process step or process condition, test requirement or any other relevant parameter that directly influences the quality attributes of the food additive or GRAS substance and which must be controlled within predetermined criteria.

Quarantine
The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Raw Material
A general term used to denote starting materials, reagents and solvents intended for use in the production of intermediates or food additives and GRAS substances.

Record
Document stating results achieved and/or providing evidence of activities performed. The medium may be paper, magnetic, electronic or optical, photographic, etc. or a combination thereof.

Re-Evaluation Date (Retest Date)
The date when the material should be re-examined to ensure that it is still in conformance with the specification.

Reprocessing
Repetition of an activity that is a normal part of the manufacturing process and that has been documented previously.

Retrieval
Process for the removal of a food additive or GRAS substance from the distribution chain.

Reworking
Subjecting previously processed material that did not conform to standards or specifications to processing steps that differ from the normal process.

Sanitize
Adequately treating food-contract surfaces by a process that is effective in destroying vegetative cells of pathogens, and in substantially reducing numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer. (21 CFR 117.3).

Sanitization
The use of sanitizing processes or chemicals to provide adequate cleaning and protection against microorganisms.

Specification
A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the tests described for a material.

Stability
Continued conformance of the food additive or GRAS substance to its specifications.

Traceability
Ability to determine the history, application or location that is under consideration (e.g., origin of materials and parts, processing history or distribution of the product after delivery).

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