PROCESS MANAGEMENT MANUAL TO ASSESS THE SAFETY OF FOOD/FEED DERIVED FROM BIOTECHNOLOGY PLANTS

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PREFACE

This manual recommends a process management system that can be used as a tool for identifying the critical areas that must be defined, controlled, and maintained during the core process of safety assessments of foods and feeds derived from biotechnology plants. It is intended as a technical tool for regulatory officials and applicants, particularly in developing countries, as a guide and reference source.

This manual has been developed using "Process Management" as a tool for the control processes, procedures, and activities to streamline operations and achieve proper balance of control processes and ability to perform work. This manual is a blueprint for the establishment of an ISO-like food/feed safety system. It includes the sequence of procedures and activities that define the "how," "what," "when," and "where" that must be followed. The activities are directly linked with the flowcharts, which provide a visual representation of each procedure.

The critical procedures described are (1) consultation, (2) premarket application, (3) food/feed safety evaluation, (3) confidential information, (4) data evaluation, (5) handling of submissions, (6) review and decision-making processes, and (7) appeal of decisions. Different annexes/requirements have been included for specific cases with the intention of not duplicating the procedures that are common for both food and feed.

The first procedure is consultation between regulatory officials and the applicant to ascertain the amount and kind of data required to address safety. This is an early discussion between the applicant and the government authority. Applicants must assume that, in the assessment process, other areas not addressed in the initial consultation may arise. The applicant provides a summary of the food/feed safety data and information. With this information, the government agency working with the developers can identify the safety and regulatory issues of specific importance to a given food/feed derived from biotechnology.

In some countries, consultation exists, but in an informal way. This manual recommends that consultation be mandatory. The premarket application provides regulatory officials with data and information to ensure the integrity of the food/feed safety assessment. For both consultation and premarket application procedures, the use of confidential information may need consideration; thus, confidential information is addressed as a separate and specific procedure.

Another critical procedure is the scientific evaluation of the data. This evaluation includes, but is not limited to, considerations of substantial equivalence, nutritional concerns, allergenicity, and toxicity. If the outcome of the evaluation is negative, the applicant may appeal the decision through an appeal procedure that is proposed in this manual.

This manual has been developed while taking into account the relevant international guidelines of the Codex Alimentarius Commission, the United Nation's Food and Agricultural Organization (FAO), World Health Organization (WHO), the Organization for Economic Cooperation and Development (OECD), and national frameworks for food safety determinations.

This manual recommends that the process of safety assessment be supported by operational and support procedures.

Operational Procedures:

- Consultation for food/feed derived from biotechnology plants
- Confidential information evaluation and handling
- Premarket application for food/feed derived from biotechnology plants
- Scientific evaluation for food/feed derived from biotechnology plants
- Appeal procedure

Support Procedures:

- Document control
- Record control

ACKNOWLEDGEMENTS

We would like to thank the following individuals for contributing to the revision of this manual:

Jeff Wolt
Risk Assessment
Biosafety Institute for Genetically Modified Agricultural Products
BIGMAP, Iowa State University

Quentin B. Kubicek
Food Safety and Ag Health Specialist
Inter-American Institute for Cooperation on Agriculture
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Food and Drug Administration

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1. INTRODUCTION

Foods are generally considered safe, provided that care is taken during their development, primary production, processing, storage, handling, and preparation. Foods are complex mixtures of compounds characterized by wide variation in composition and nutritional value.

Although modern biotechnology broadens the scope of genetic modifications (GM) that can be introduced into plants used for food/feed, it does not inherently result in foods/feed that are less safe than those produced by conventional techniques. This principle has been widely endorsed by numerous scientific bodies, such as the WHO, CODEX, and the FAO; and it means that a new or higher standard of safety is not required for these new foods and that previously established principles for assessing food safety still apply.

In most countries where genetically engineered (GE) food/feed products have been marketed, regulatory regimes have been specifically established to assess the safety of GE food/feed products. Central to all of these systems is a risk assessment framework that takes a comparative approach to establishing the safety of the new product relative to an accepted counterpart food. A fundamental consequence of this approach is that products that have received regulatory approval are viewed to be "as safe as" their conventional counterparts.

Food and feed products derived from biotechnology are now being commercialized and marketed around the world; therefore, many countries have established appropriate approaches for their safety assessment of these products. Additionally, CODEX has developed general principles for risk analysis of foods derived from modern biotechnology. In recognition of these emerging global standards, we consider here three common elements of GE food/feed safety assessment for the purposes of regulatory approval:

1. the general framework for risk analysis,
2. principles of food safety assessment, and
3. regulatory goals for food safety determination.

1.1 The general framework for risk analysis

The concepts and principles of safety of food and food ingredients are equally applicable to foods and food ingredients derived from biotechnology. The potential hazards associated with foods and the associated risks from dietary exposure to food items are subject to the risk analysis process.

Risk analysis is a structured approach, comprising three distinct but closely linked components:

1. risk assessment,
2. risk management, and
3. risk communication.

Risk assessment is the scientific evaluation of known or potentially harmful health effects. The risk assessment process seeks to determine the probability of harm posed by exposure to a food

form, and the process includes distinct steps. The first step is "hazard identification," which is designed to identify whether a hazard—a nutritional or other safety concern—is present and to gather information on its nature and severity. The hazard assessment should include a comparison between a food/feed derived from biotechnology and its conventional unmodified counterpart, if this exists, and should seek to determine their similarities and differences. If a hazard is identified, a comprehensive "hazard characterization" is conducted. The hazard characterization involves the qualitative and/or quantitative evaluation of the nature of the adverse effects associated with biological, chemical, and physical agents that may be present in food. Risk assessment also includes "exposure assessment," which evaluates from a qualitative and/or quantitative perspective the degree of dietary intake likely to occur. The hazard and exposure characterization are integrated into the "risk characterization," which is the culmination of the above steps to estimate the risk or to determine if additional data is needed to calculate the risk.

Risk management is the process of considering alternatives to accept, minimize, or reduce assessed risks and to select and implement appropriate measures for the mitigation (reduction) of risk. Risk management may include a preliminary risk management decision followed by assessment of risk management options, monitoring, and review of the decision taken. The preliminary risk management activities include identification of the food safety problem, establishment of risk policy, and consideration of the risk assessment result. The risk management process should be transparent, consistent, and fully documented. Specific tools may be needed to facilitate the implementation and enforcement of measures, including the development of appropriate analytical methods, provision of reference materials, and development of protocols for the potential tracing of the product to facilitate its withdrawal from the market if an adverse effect is subsequently identified.

Finally, risk communication seeks clear, interactive, and well-documented communication among risk assessors, managers, consumers, the academic community, and other interested parties covering aspects of the risk analysis process. An important element of risk communication is respecting legitimate concerns to preserve the confidentiality of information. The risk communication process should provide a sound basis for understanding the risk assessment and management actions taken to enhance trust and confidence in the safety of the food supply. Risk communication should include the dissemination of information and should take into account, within the decision-making process, comments received from the public.

Generally, consumers consider that traditional foods that have been eaten for years are safe and that those derived from biotechnology are recent and thus require special attention. Therefore, the majority of national authorities have set up a specific system for the rigorous evaluation of foods/feed derived from biotechnology prior to marketing. The primary intent of these national systems is to determine the safety of GE-derived foods/feed relative to their conventional non-GE counterparts.

A transparent and well-defined regulatory framework should be provided in assessing, managing, and communicating the risk associated with foods and feed derived from biotechnology. A consistent approach should be adopted to characterize and manage safety and nutritional risks associated with foods/feed derived from biotechnology or any other method of production. The acceptable level of risk for foods/feed derived from biotechnology plants should

be consistent with that for similar foods/feed already on the market.

According to principles elaborated by CODEX and the WHO, foods pose three types of risk to human health: they can potentially contain allergens, toxins, or antinutrients. Therefore, scientists who evaluate food safety recognize that conventional food or foods derived from biotechnology cannot be guaranteed to pose zero risk.

The primary concern with food derived from biotechnology, with respect to human health, is the potential for unintentional introduction of a new allergen, an enhanced toxin, or an enhanced antinutrient in an otherwise safe food.

Primarily, the safety assessment should include a comparison between foods derived from biotechnology plants and their conventional counterparts, considering their similarities and differences. The comparison should be done with the whole food or a relevant food component, taking into accounts the intended or unintended effects and changes in key nutrients relevant to human/animal health.

In particular, the safety assessment of foods derived from biotechnology should address:

- toxicity,
- allergenicity,
- specific components thought to have nutritional or toxic properties,
- the stability of the inserted gene,
- the nutritional effects associated with genetic modification and
- any unintended effects which could result from the genetic construct.

1.2 Principles of food safety assessment

Safety is the determination of the acceptability of a given level of risk. The existing food supply has a long history of safe use, even though some foods are not safe for some individuals and many foods contain substances with accepted levels of risk. Society accepts these as safe, given their history of consumption. Currently, foods derived from biotechnology have been obtained from traditional crops (corn, soybeans, potato, and cassava). Our collective knowledge and experience gained in the traditional use of these crops is an important component in the safety assessment of foods derived from biotechnology.

The concept of "substantial equivalence" has been well established as an important component in environmental, health, and food safety assessment. The concept is based on the idea that an existing plant/crop used as food or as a source of food, can serve as the basis for comparison to assess the safety for human health of a food or food form derived from biotechnology. The determination of substantial equivalence commonly includes comparisons of agronomic performance, plant phenotype, composition (macro- and micro-nutrients), and amounts of antinutrients and natural toxicants. The determination identifies similarities and differences between the product derived from biotechnology and its conventional counterpart. This approach acknowledges that the goal of the assessment is to establish a relative standard for safety based

on the consideration as to whether the food derived from biotechnology is as safe as its traditional counterpart, where such a counterpart exists.

The application of the substantial equivalence concept does not comprise a safety or risk assessment in itself, since it does not characterize the hazard due to the GE product. Rather, it is used as a key initial step in the safety determination process of food derived from biotechnology, which takes into account both intended and unintended effects, identifying new or altered hazards, and identifying changes relevant to human health in key nutrients. Should a product be shown to be not substantially equivalent, the assessment would focus on the parameters shown to be not substantially equivalent and the risks thereof.

The safety evaluation typically includes identification of the composition and structure of the gene product(s); quantification of each gene product expressed in the food; a search for similarity to known toxins, anti-nutritional factors, allergens and other functional proteins; a determination of the thermal and digestive stability of each gene product; and the results of the toxicological assays to determine allergenicity and toxicity. Thus, the food safety evaluation for a food derived from biotechnology is in essence a risk assessment. The standard for comparison is knowledge of a conventional food counterpart, its safety, and the acceptability of the degree of comparative risk that is identified.

The safety assessment for whole foods is case by case, based on an evaluation of multi-disciplinary data and information of agronomic, genetic, molecular biological, nutritional, toxicological and chemical properties. The first step in the safety assessment is the characterization of each genetic construct, including the identification of the donor(s) of the genetic material. This allows the risk assessment to establish if the genetic material originates from a pathogenic, toxin-producing, or allergenic source.

Additional aspects considered in the evaluation are the new gene(s), the new protein(s) or other gene products, and possible effects on other food components. Intended and unintended changes in the food must be taken into account and steps must be taken to reduce the likelihood of adverse and unexpected effects. Toxicological tests of animals may be conducted to address specific issues arising from the data evaluation.

Since genetic modifications may involve the introduction of new genes into the recipient plant, which could produce new proteins, the potential allergenicity of these new proteins must be a key factor in the safety assessment. This assessment should include consideration of whether the new protein is one that certain individuals may already be sensitive to or is one that may be likely to induce allergic reactions in some individuals. As there is no definitive test to predict allergic response to a new protein in humans, it is recommended that an integrated, stepwise, case-by-case approach be used in the assessment of possible allergenecity of a newly expressed protein. The initial assessment should include the determination of:

- the sources of the introduced genetic elements;
- any significant similarity between the amino acid sequence of the new protein and that of known allergens; and
- the susceptibility of the new protein to enzymatic degradation, heat stability,

and/or acid treatment.

1.3 Regulatory goals for food/feed safety determination

The overall regulatory goal of a premarket safety assessment is to minimize reasonable, anticipated, potential adverse effects from food or feed derived from biotechnology plants. The risk management measures for food/feed derived from biotechnology should be proportional to the risk and based on the outcome of the risk assessment. Risk management measures may include conditions for market approval, post-market monitoring, labeling, and development of analytical methods for the detection or identification of foods or ingredients derived from biotechnology. In the process of obtaining market approval, the applicant submits scientific data and information that are generally obtained from different sources, such as the developer of the product, scientific literature, general technical information, regulatory agencies, international bodies, and other parties. These and any other data should be assessed using appropriate science-based risk assessment methods. The testing procedures should be scientifically sound and the parameters measured should be comparable.

The need for post-marketing monitoring may be an appropriate risk mitigation measure in specific circumstances but should only be considered on a case-by-case basis. No international consensus exists as to whether post-monitoring studies are technically possible and cost-effective in order to provide meaningful information regarding safety. Therefore, regulatory decision-making needs to be judicious in the determination to require post-monitoring studies. The value of this measure is to verify that the safety process is working as intended and to detect any cases of noncompliance.

Risk communication is very important at all phases of risk assessment, and it is an interactive process that involves industry, government, scientists, media, consumers, and academia. Risk communication should provide transparency during the safety assessment and management decision-making processes. It is necessary to implement a public system of communication observing the legitimate concerns to safeguard the confidentiality of information.

Since feed represents an important point of entry of plant products into the food chain, feed safety assessment is relevant to overall food safety. Developers should address GE feed with particular attention to the intended feed uses, the species consuming the feed, the function and level of all introduced or modified substances, any changes in the composition and characteristics of the feed, and resulting food derived from the animals that consume the feed.

The safety assessments of food and feed derived from biotechnology plants share many common elements, particularly the molecular characterization of the introduced genetic elements, the expression of novel traits and the impact of these traits in the newly modified plant, evidence of intended/unintended effects occurring due to each insertion, and a comparison to the plant's unmodified counterpart. The assessment of feed must take into account any risk to the animal consuming the feed and to the consumers of animal products such as meat, milk, or eggs.

Animals are often fed unprocessed raw plants and components of plants that humans do not consume; thus, the exposure of animals to novel genes and their products is different from that of

humans. The nature of genetic modification may be of relevance only to animal feeding, as in the case of forages. In processed feed, DNA or protein may be difficult to detect as it is often degraded by typical feed manufacturing processes. Nevertheless, any novel protein should be examined for its allergenic and toxic potential to humans, regardless of its susceptibility to breakdown. Animal performance studies are frequently conducted to address many of the questions arising from the feed safety assessment.

2. PROCEDURE FOR CONSULTATION FOR FOOD/FEED DERIVED FROM BIOTECHNOLOGY PLANTS

The consultation procedure is intended to ensure that food/feed safety and other regulatory issues are resolved at a very early stage of development and prior to market introduction. It is an early opportunity for developers to meet with government authorities (GA) to discuss anticipated and potentially new regulatory issues for a new food/feed derived from biotechnology plants. The GA will review the initial data in consultation with the developer. If the data suggests potential regulatory or safety issues, the GA would notify the developer of these. Herein lies the value of a premarket consultation: it saves resources and time by assuring that a petition contains the necessary information for the GA to conduct an assessment. While additional information may be required later by the GA, the initial consultation would provide guidance as to the kind and detail of information required.

The consultation format requires information and data sufficient to characterize the food/feed. It enables the GA to analyze and discuss with the applicant safety issues pertinent to the applicant's submission. At this early stage, relevant information includes the identity and intended effect of the transformation event and the source of each transgene. This information allows the GA to address potential health risks of the transformation event being an unapproved food/feed additive and which may require discussions with other pertinent GAs. The source of the genetic material would permit the GA to identify issues associated with allergenicity, pathogenicity, and toxicity.

The first activity of the GA is to receive a request for a consultation and create a public file record. The GA would take into account the data or information claimed by the applicant as confidential. If the consultation includes confidential information (CI), the applicant would follow CI procedures.

During the consultation, if it is determined that the food/feed derived from biotechnology plants contains an introduced pesticide, or affects pesticide use or changes, the GA would discuss this with other pertinent GA that may have the responsibility under their specific regulations. Pesticide may have environmental concerns that need to be addressed separately.

In order to meet the GA requirements of transparency, the GA will make publicly accessible the record file, excluding CI. The GA will use available public systems of information to ensure that the public is aware of the consultation and the decision-making process.

CONSULTATION FOR FOOD/FEED DERIVED FROM BIOTECHNOLOGY PLANTS

GOVERNMENT AUTHORITY

Authorization Date	
Effective Date	
Created by	
Approved by	

1. Purpose:

1.1 The objective of this procedure is to define the sequence of events, interfaces, and responsibilities involved in submitting a petition for consultation of a food/feed derived from biotechnology plants.

2. Scope:

2.1 From submission of a petition for consultation of a food/feed derived from biotechnology plants to discussions of the potential regulatory and scientific issues.

3. References:

3.1 Biosafety regulations
3.2 National food/feed safety regulations
3.3 Consultation details
3.4 Data/reports, other statistics
3.5 CODEX Alimentarius standards
3.6 Guidelines for the conduct of food/feed safety assessment of food/feed derived biotechnology plants

4. Definitions:

4.1 GE: Genetically engineered
4.2 GM: Genetically modified
4.3 GA: Government authority, agency responsible for food/feed safety assessment
4.4 FBC: Food Biosafety Committee, advisory committee
4.5 OECD: Organization for Economic Cooperation and Development
4.6 CODEX: Food Standards; collection of standards, codes of practice, guidelines and other recommendations
4.7 CI: Confidential Information; includes trade secrets, commercial, financial, biosafety or other information that the applicant deems necessary to keep from public access
4.8 PIS: Public Information System
4.9 Consultation: early discussion between the applicant and GA
4.10 Consultation Number: number defined and assigned by GA

5. Responsibility and Authority:

5.1 The ____ of GA is responsible for receiving and registering petitions for consultations.
5.2 The ____ of GA is responsible for administratively reviewing the consultation.
5.3 The ____ of GA is responsible for discussing with other agencies in the case of pesticides.
5.4 The ____ of GA is responsible of analyzing the application's preliminary data and information.

5.5 The ____ of GA is responsible of making a recommendation report of the application's data and information.
5.6 The ____ of GA is responsible for providing the applicant of the recommendation report.
5.7 The ____ of GA is responsible for public communicating through a PIS receipt of petitions for consultation.

6. Activities:

6.1 Receive petition for consultation
- 6.1.1 The ____ of GA receives petition for consultation (Annex A) and creates a record file (Annex B).
- 6.1.2 The _____of GA will establish a record file number using …… (BIOFOOD) and numbers related with the date of receipt. (Annex C).
- 6.1.3 If the petition contains CI the ____ of GA follows procedure for CI evaluation and handling.

6.2 Review preliminary data
- 6.2.1 The ____ of GA will review preliminary data in a period of five working days before notifying applicant of a consultation date, making a report of revision (Annex D).
  - 6.2.1.1 If the consultation requires further information, continue with 6.3.
  - 6.2.1.2 If the consultation is considered adequate related to a pesticide, continue with 6.4
  - 6.2.1.3 If the consultation is considered adequate and is not related to a pesticide, continue with 6.5

6.3 Notify for more information
- 6.3.1 The ____ of GA will notify the applicant through a memorandum in a maximum of 5 working days of the information required to begin the review. (Annex E).

6.4 Discussion with other agencies
- 6.4.1 If necessary, the ____ of GA will discuss with other agencies any pesticide-related issues and prepare for the file record a report of their consultations.

6.5 Analyze consultation
- 6.5.1 The ____ of GA will analyze the consultation and prepare a report following the technical aspects (Annex F).

6.6 Response to applicant
- 6.6.1 The ____ of GA will notify the applicant of the information that is required by the GA to address safety concerns (Annex G). The ____ of GA will notify the applicant within xx days.
- 6.6.2 The ____ of GA will record the consultations (Annex H).

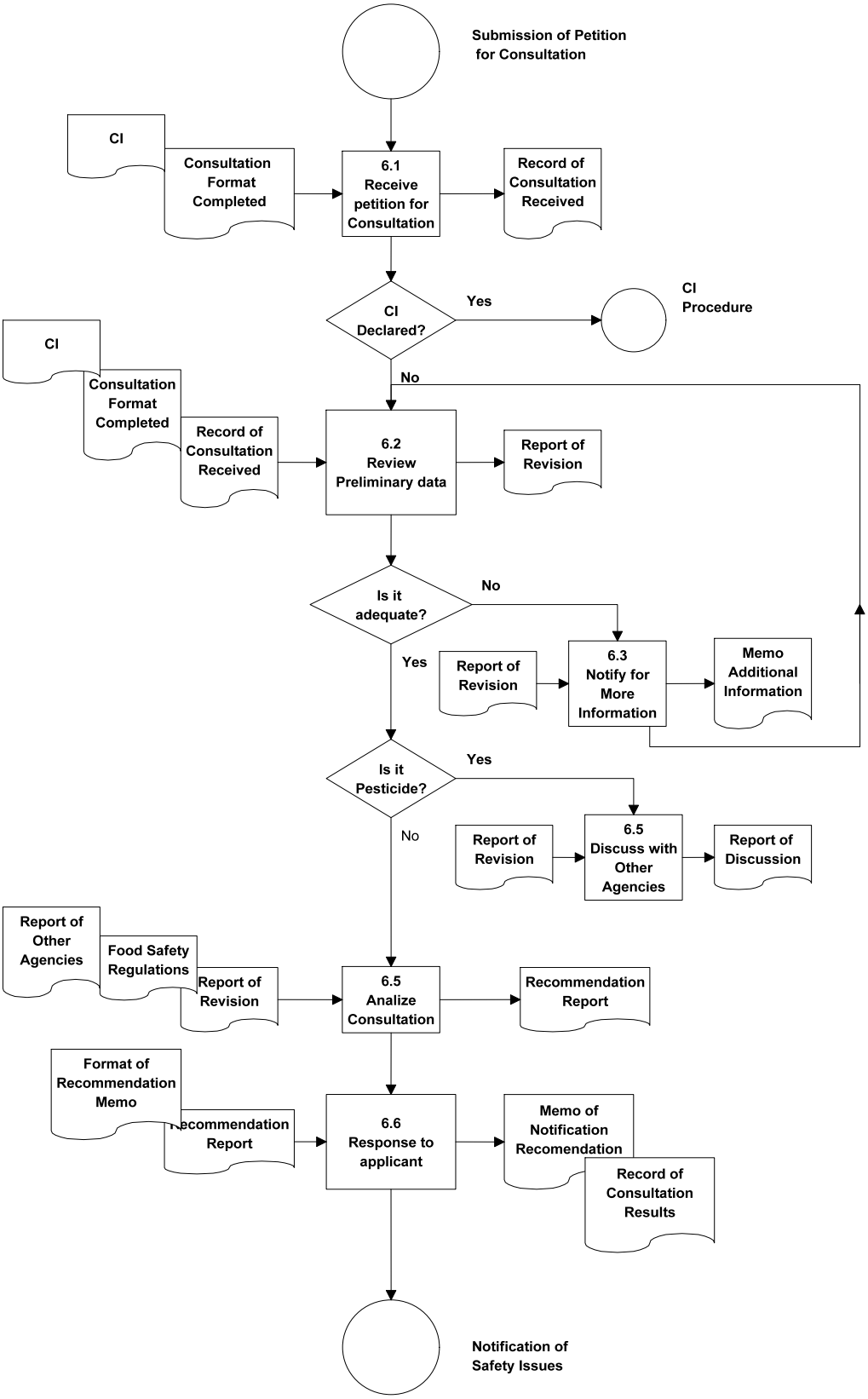
7. Records:

7.1 Record of petition for consultation received.
7.2 Record of revision report
7.3 Record of analysis report
7.4 Record of PIS selected

8. Flowchart and Annexes:

8.1 Flowchart
8.2 Annex A: Format: Consultation Request
8.3 Annex B: Format: Convening Meeting Memo
8.4 Annex C: Format: List of Consultations Received by GA
8.5 Annex D: Format: Report of Revision
8.6 Annex E: Format: Memo Requesting Additional Information
8.7 Annex F: Format: Safety Assessment Summary Report
8.8 Annex G: Format: Recommendation Memo
8.9 Annex H: Record of Consultations

CONSULTATION FOR FOOD/FEED DERIVED FROM BIOTECHNOLOGY PLANTS FLOWCHART



ANNEX A

Format: Consultation Request

To: ____ of GA

From: Applicant/ Developer Name, Address/Tel/Fax/e-mail

Date: MM/DD/YY

Pursuant to the regulations, we hereby request a consultation to discuss scientific and regulatory considerations of an application we are considering submitting to your office. Enclosed is a summary of preliminary safety and nutritional data that we have conducted regarding the GM food/feed.

- Name of the GM food/feed and crop from which it is derived
- Description of applications or uses of the GM food/feed
- Information of the sources, identities, and functions of each introduced genetic material
- Information on the purpose or intended effect of the modification and its expected effect on the composition or properties of food/feed
- Information on the identity and function of expression products encoded by each introduced genetic material
- Information regarding any known allergenicity and toxicity of expression products and the basis for concluding the safety human/animal consumption
- Information on the comparison of the composition of the GM food/feed with the food derived from the parental variety in relation with important nutrients and toxicants that occur naturally in the food
- Any other information relevant to the safety and nutritional assessment of the bioengineered food

_____
APPLICANT SIGNATURE

Date Received:	Consultation Number:

ANNEX B

Format: Convening Meeting Memo

To: Applicant

From: GA

Date: MM/DD/YY

We are in receipt of your request of MM-DD-YY for a consultation. The meeting will take place on MM-DD-YY starting at 9:00am. For further information, contact XYZ of our office at (123) 456-7890 or by Email at XYZ@GA.gov.

_____

GOVERNMENT AUTHORITY SIGNATURE

ANNEX C

Format: List of Petitions for Consultation Received by GA

(GA Internal Use)

Consultation number	Date received	Use: food, feed, both	Gene/gene product	Source of gene(s)	Intended effect	Designation of transformation event;OECD unique identifier	Applicant

ANNEX D

Format: Report of Revision

- Applicant name, address, telephone number, email
- Consultation number
- Name of food/feed derived from biotechnology plants
- Recipient plant species (scientific and common names)
- Designation of transformation event
- Identity and source of gene(s)
- Purpose or intended effect
- Changes expected in food/feed composition characteristics
- Intended food uses
- Intended feed uses

ANNEX E

Format: Memo Requesting Additional Information

To: Applicant

From: GA

Consultation number:

Date: MM/DD/YY

After revision of your submission, we request THAT YOU PROVIDE ADDITIONAL information or clarification concerning the following areas:

_____
_____
_____

Upon receipt of your information, our review will renew.

_____
GOVERNMENT AUTHORITY SIGNATURE

ANNEX F

Format: Safety Assessment Summary Report

- Consultation number
- Identification of transformation event
- Food additive status
- Allergenic potential
- Safety status of protein/additive
- Result of comparison with conventional/counterpart food/feed
- Pesticidal nature
- Information from other agencies
- Changes in the composition/characteristics of the food/feed
- Intended use

ANNEX G

Format: Recommendation Memo

To: Applicant

From: GA

Consultation number:

Date: MM/DD/YY

With regard to your consultation number _____ and based on the description of data and information presented throughout the consultation process, **this Agency (mark one):**

____ has no additional questions concerning your submission at this time.

____ requires clarification on the following areas:

1) _____

2) _____

Please provide the requested information at your earliest convenience; upon receipt of your information, our review will renew.

_____
GOVERNMENT AUTHORITY SIGNATURE

ANNEX H

Record of Consultation

Consultation number	Date request received	Date consultation held	Use: food, feed, both	Gene/gene product	Intended effect use phenotype	Designation of transformation event (OECD unique identifier)	Applicant

3. PROCEDURE FOR EVALUATING AND HANDLING CONFIDENTIAL INFORMATION

Confidential information (CI) includes trade secrets, commercial, financial, biosafety, or other information that the applicant deems commercially valuable, used in the business and maintained in secrecy. Trade secrets include any commercial plan, formula, process, or device that is used for making, preparing, compounding, or processing of a trade product, and there is a relationship between the trade secret and the productive process. Commercial or financial information should be considered confidential if substantial competitive harm would result from disclosure. Biosafety information may be kept confidential if disclosure of this information would lead to destruction or vandalism. Applicants that claim CI must provide written justification. The GA will determine the validity of the justification and inform the applicant in the event the GA disagrees. Therefore, it is necessary to establish procedures for handling CI to ensure identity security, physical security, and handling of and access to the documents. Applicants must provide the GA with a non-CI copy. A non-CI copy is a reproduction of the CI copy with the CI having been blacked out from the text and each page clearly marked with "CI deleted" in bold and enlarged text.

The GA will designate an official staff that will have the responsibility of handling and controlling access to documents containing CI. The GA must also implement a mechanism to assure the storage of the documents; for example, the documents may be placed in locked areas or may use alarm activation, file systems, or other appropriate means.

Sometimes, during the evaluation of the premarket application, Food/Feed Biosafety Committee members and Agency reviewers will need to review CI information. As a result, the GA must maintain a list of who is able to access CI documents. These persons should receive training on safeguarding CI before obtaining access to CI documents. Each person is responsible for securing the CI documents while in their possession during the revision process. They shall not reveal or allude to any data or information deemed CI in the biosafety reports. The GA will provide secure/private areas where CI documents may be reviewed.

EVALUATING AND HANDLING CONFIDENTIAL INFORMATION PROCEDURE

GOVERNMENT AUTHORITY

Authorization Date	
Effective Date	
Created by	
Approved by	

1. Purpose:

1.1 The objective of this procedure is to define the sequences of events, interfaces, and responsibilities involved in the procedure of evaluating and handling CI.

2. Scope:

2.1 From the submission of a consultation/premarket application containing CI to the secure handling and storage of CI documents.

3. References:

3.1 National Regulations on the Protection of Confidential Information

3.2 List of personnel authorized to receive CI

4. Definitions:

4.1 GA: Government Authority

4.2 FBC: Food Biosafety Committee

4.3 CI: Confidential Information: includes trade secrets, commercial, financial, biosafety or other information that the applicant deems necessary to keep from public access

5. Responsibility and Authority:

5.1 The ____ of GA is responsible for receiving and registering CI documents.

5.2 The ____ of GA is responsible for evaluating and acceptance of the applicant's claims for CI.

5.3 The ____ of GA is responsible of storing and safe handling of CI documents and designating who may have access to CI.

5.4 Persons with access to CI are individually responsible for securing any CI documents during a revision and maintaining its confidentiality.

6. Activities:

6.1 Receive CI

6.1.1 The ____ of GA will file date of receipt of a premarket application containing information that the applicant claims to be CI.

6.1.2 The ____ of GA will identify and mark a CI and non-CI copy and record (Annex A).

6.1.3 The ____ of GA will authorize GA personnel who will be responsible for handling CI.

6.2 Evaluate applicant claims for CI

6.2.1 The ____ of GA will evaluate applicant's claims for justifying CI (Annex B) in a maximum of 10 working days.

6.2.1.1 If CI claims are not accepted, continue to 6.3.

6.2.1.2 If CI claims are accepted, continue to 6.4

6.3 Notify non-acceptance of claims for CI

6.3.1 The ____ of GA will notify the applicant of the non-acceptance of the CI claim (Annex C) in a maximum of 10 working days.

6.3.2 The applicant may appeal the GA's decision by following the appeal procedure.

6.4 Notify acceptance of claims for CI

6.4.1 The ____ of GA will notify the applicant the acceptance of the CI claim in a maximum of 10 working days (Annex D).

6.5 Storage of CI

6.5.1 Designated GA personnel will store CI in a secure area when it is not used.

6.6 Authorize access to CI

6.6.1 The ____ of GA will designate who is allowed to review CI and prepare a list of these authorized persons (Annex F).

6.6.2 Authorized personnel of the GA will restrict access to CI to only those persons on the GA's designated list.

6.6.3 The ____ of GA will record date/time of receipt and return of CI documents (Annex E).

6.6.4 The ____ of GA will take precautions so that unauthorized persons are not present at meetings where CI is discussed.

6.6.5 Authorized personnel are individually responsible for maintaining the confidentiality of the information.

6.6.6 Authorized personnel will prepare their reports without revealing any confidential information.

6.6.7 The ____ of GA will train authorized experts on safeguarding CI before giving authorized status.

6.6.8 The _____ of GA will provide private working areas for receiving CI documents.

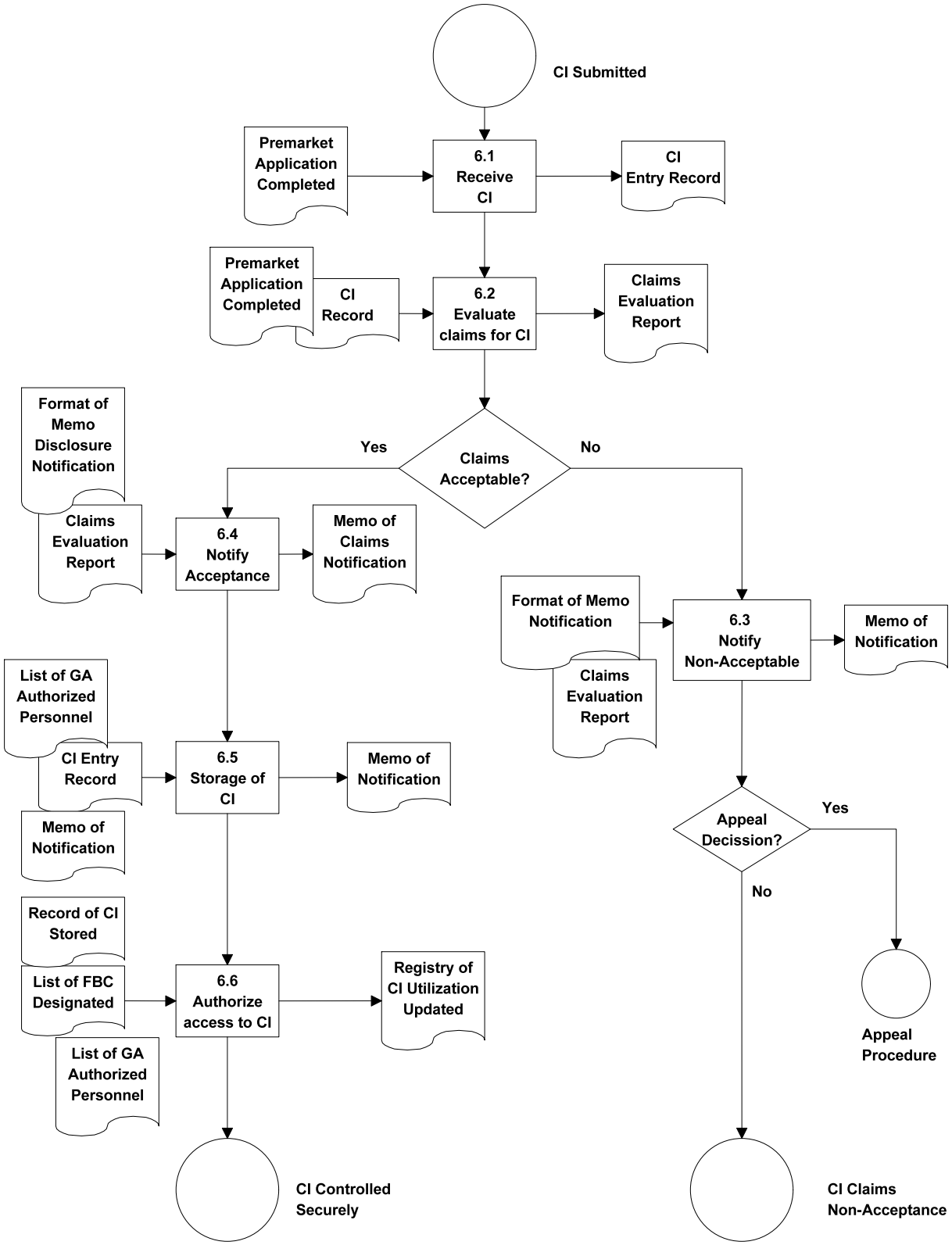
7. Records:

7.1 Record of receipt and date of premarket application with CI
7.2 Evaluation report
7.3 List of designated experts
7.4 Registry of CI utilization
7.5 List of authorized personnel

8. Flowchart and Annexes:

8.1 Flowchart
8.2 Annex A: Format: Receipt of Confidential Information
8.3 Annex B: Format: Evaluation Report
8.4 Annex C: Format: GA Notification of Denying Claims for CI
8.5 Annex D: Format: Notification of CI Acceptance
8.6 Annex E: CI Utilization Registry
8.7 Annex F: List of Authorized Personnel to Receive CI Copy of Premarket Application Number

EVALUATING AND HANDLING CONFIDENTIAL INFORMATION FLOWCHART



ANNEX A

Format: Receipt of Confidential Information

(GA Internal Use)

Consultation/Premarket application number	**Date of receipt (MM/DD/YY)**	**Page number(s) having CI**	**Total number of pages with CI**	**Staff name**	**Signature**
xyz123	11/12/05	5,17,43,167	4		

ANNEX B

Format: Evaluation Report

(GA Internal Use)

Premarket Application #:

Applicant Name:

The following information claimed as Confidential Information in premarket application # (page numbers: 17 and 54) _____ is not accepted as CI because:

_____
_____
_____
_____
_____

ANNEX C

Format: GA Notification Denying Claims for CI

Premarket Application #:

Date:

To: Applicant:

From: Government Authority

You are hereby informed that the following claim(s) for CI in your premarket application # has/have not been accepted:

_____

_____

The GA has conducted an examination of each confidential information claim you made in premarket application # xyz123. The GA does not accept the validity of the following claims for CI and the information is not entitled to confidentiality. The GA believes the information you claim as CI is publicly available (*other reasons may be given here). You have the option of appealing this decision; please note that you bear the burden of substantiating the confidentiality of your claims. Your appeal to this determination must be postmarked by MM-DD-YY (10 working days from the date of this letter). If an appeal is not received the Agency will consider the information as not entitled to confidential treatment and may be subject to public disclosure. You may appeal by following the established appeal procedure.

You may opt to provide further justification for each of the above claims. Please provide the GA with amended/corrected pages which reflect the changes in CI status. Upon receipt of the amended/corrected pages, our review of your application will renew.

_____

GOVERNMENT AUTHORITY SIGNATURE

ANNEX D

Format: Notification of CI Acceptance

Premarket Application #:

Date:

To: Applicant

From: Government Authority

You are hereby informed that your claims for CI contained in application # have been accepted.

_____

GOVERNMENT AUTHORITY SIGNATURE

ANNEX E

CI Utilization Registry of Premarket Application Number

Date out (MM/DD/YY)	Date in (MM/DD/YY)	Authorized user	Designated expert	Staff name and signature

ANNEX F

List of Authorized Personnel to Receive CI Copy of Premarket Application Number

Name	ID	Address	Institution	Date authorized (MM/DD/YY)	Signature

4. PROCEDURE FOR PREMARKET APPLICATION FOR FOOD/FEED DERIVED FROM BIOTECHNOLOGY PLANTS

When an applicant has accumulated sufficient information and believes it is adequate to ensure that the food/feed derived from biotechnology plants complies with the safety regulations, the applicant may submit a premarket application to the GA responsible for ensuring the safety of food/feed prior to introduction into the market.

In this premarket application, the GA requires data and information regarding the safety of the product that would be consumed by humans or animals.

The GA will receive a premarket application that includes data and information about the safety of the product. The application will include those data plus assessments requested as a result of the premarket consultation procedure. The application may include information and data from environmental releases and safety assessments conducted in other countries. The applicant will send an original application and copies by paper or electronic mail.

The safety assessment is focused on the identification of new and altered hazards in relation to the conventional counterpart, taking into account the intended and unintended effects of each genetic construct. The safety assessment should include data and information to reduce the uncertainties that the food/feed derived from biotechnology plants will have an unexpected or adverse effect on human or animal health. The goal of each safety assessment is to provide scientific knowledge of the data and information that the food/feed does not cause harm when prepared, used, and/or eaten according to its intended use.

Some information included in the premarket application form, such as a description of the GE, should be sufficient to aid in understanding the nature of the food/feed submitted for safety assessment. It is important to determine if the donor organism(s) presents characteristics of allergenicity, pathogenicity, or toxin production that could affect human or animal health. In order to provide clear understanding of the impact on the composition and safety of food/feed derived from biotechnology plants, a comprehensive molecular and biochemical characterization of the genetic modification should be carried out.

The toxicological requirements for food/feed derived from biotechnology must be considered on a case-by-case basis and will be determined in part by comparison with the conventional counterpart and by the intended uses. All studies should be conducted using nationally or internationally agreed protocols, such as the Principles of Good Laboratory Practices.

Information about the potential for the accumulation of metabolites in the food/feed should be given in the premarket application; therefore, where altered residue and metabolite levels in such food/feed are identified, it would be necessary to evaluate the potential impact on human/animal health.

Information describing the processing conditions or methods used in the production of the food/feed or ingredient derived from biotechnology plants, if they are different than that for their conventional non-transformed counterpart, must be provided.

Information on the potential allergenicity of the expressed protein should be provided. The assessment of allergenicity should be based on the following:

- The donor organism(s) of the genetic construct, particularly if the donor organism(s) is/are known to cause allergies
- Comparison of the amino acid sequence of the newly introduced protein with known allergens
- The physiochemical properties of the newly introduced protein, effect of pH, digestion, heat and processing stability.

Similar information is required for animal feed applications as is required for foods, such as the molecular characterization of the introduced genetic elements, the expression of the novel traits, and the impact of these traits on the newly modified plants. Establishing the degree of equivalence with the conventional varieties is an important starting point for food/feed safety issues.

The GA will record date of receipt of the premarket application and give it a file number. The GA will then review the completeness of the application administratively; if it is not complete, the GA will notify the applicant of any additional information required. The GA will evaluate claims for CI and notify the applicant of rejected claims.

When the application contains sufficient information to demonstrate that the applicant has addressed all matters relevant to the safety and regulatory issues of the foods/feed derived from biotechnology plants, the GA will begin its safety assessment. In the event the GA does not consider itself to have enough in-house expertise to assess an application, the GA may seek the assistance of outside experts. In these cases, this Manual recommends that the GA convene a Food/Feed Biosafety Committee (FBC) of experts from consumer, scientific, environmental, and nutritional sectors to provide, in their personal capacity, guidance to the GA and appropriate expertise on the data submitted by the applicant. Criteria for selecting FBC experts are provided in Annex A.

These outside experts will assist the GA in their capacity and will have access to the necessary information (including CI) required to reach a determination. The experts and the GA will collectively form FBC. The FBC is specific to a particular application and will cease to function once a determination has been made on that application. The GA will cover authorized expenses incurred by outside experts of the FBC.

Upon receipt of an application which requires the GA to form a FBC, and upon acceptance by outside experts to join the FBC, the GA will send copies of the application to each FBC member. The GA will convene a meeting for the FBC to evaluate the application. Depending on the complexities of the data, the FBC may need to have more than one meeting to complete its evaluation.

The GA will announce to the public receipt of a request for premarket application, will make publicly available the record file, and will allow for public comment. The GA will implement a formal system for publication of the premarket applications received.

The GA will take into account public comments and the FBC's evaluation when making its decision on the premarket application. The GA will communicate its decision in writing to the applicant and to the public through a public information system. The implementation of transparent communication to the public is expected to add credibility to GA procedures.

The GA's decision to deny the application or to approve with conditions may be appealed by the applicant using the appeal procedure.

PROCEDURE FOR PREMARKET APPLICATION FOR FOOD/FEED DERIVED FROM BIOTECHNOLOGY PLANTS

GOVERNMENT AUTHORITY

Authorization Date	
Effective Date	
Created by	
Approved by	

1 Purpose:

1.1 The objective of this procedure is to define the sequence of events, interfaces and responsibilities involved in the process of applying for a request to market a food/feed derived from biotechnology plants.

2 Scope:

2.1 From submission of a premarket application for food/feed derived from biotechnology to the GA's determination of safety.

3 References:

3.1 Biosafety Regulations
3.2 National Food Safety Regulations
3.3 Application details
3.4 Data/reports, other statistics
3.5 Codex Alimentarius Commission
3.6 WHO-FAO Guidelines
3.7 OECD Guidelines

4 Definitions:

4.1 GE: Genetically Engineered
4.2 GA: Government Authority
4.3 FBC: Food/Feed Biosafety Committee
4.4 OECD: Organization for Economic Cooperation and Development
4.5 CI: Confidential Information
4.6 PIS: Public Information System
4.7 WHO: World Health Organization
4.8 FAO: Food and Agriculture Organization
4.9 CODEX: Codex Alimentarius Commission

5 Responsibility and Authority:

5.1 The ____ of GA is responsible for receiving and registering premarket applications.
5.2 The ____ of GA is responsible for reviewing premarket applications administratively.
5.3 The ____ of GA is responsible for distributing premarket applications to the members of the FBC.
5.4 The FBC is responsible for evaluating the premarket application.
5.5 The FBC is responsible for preparing a technical report of the premarket application.
5.6 The ____ of GA is responsible for notifying the applicant of approval or non-approval.
5.7 The ____ of GA is responsible for communicating to the public through a public information system.

6 Activities

6.1 Receive application

6.1.1 The ____ of GA will receive the application (Annex A) and record the date of receipt (Annex B).

6.1.2 If the application contains CI, continue with the CI Evaluation and Handling Procedure

6.2 Review application

6.2.1 The ____ of GA will analyze and verify the completeness of the application, checking that all sections of Annex A have been submitted.

6.2.2 The ____ of GA will verify completeness in a maximum of five working days, filling out the application checklist/report of revision (Annex C).

6.2.3 If all the information is not included, continue with 6.3

6.2.4 If all the information is included, continue with 6.4.

6.3 Notify for more information

6.3.1 The ____ of GA will notify the applicant of required information through a memorandum (Annex D) in a maximum of five working days.

6.4 Distribute application

6.4.1 If necessary, GA will form a FBC consisting of outside experts and GA officials, based on the terms of reference established (Annex E)

6.4.2 The ____ of GA will send the premarket application to the members of the FBC with a memo (Annex F) to convene a meeting to evaluate the technical aspects of the application in a maximum of five working days.

6.5 Communicate to the public

6.5.1 The _____ of GA will make public the record through an information system (official government gazette, national, regional or local newspaper, internet site, etc.) (Annex J), without including CI.

6.5.2 The public will have 30–120 days to present comments.

6.5.3 The ____ of GA will consider comments from the public.

6.6 Evaluate application

6.6.1 The ____ of GA or FBC will evaluate the premarket application and prepare a report following public input, GA food safety regulations, and international standards and guidelines (Annex G).

6.6.2 The ____ of GA will prepare a report in a maximum of 75 days.

6.6.3 If the result of the evaluation is favorable, continue with 6.7.

6.6.4 If the result of the evaluation is unfavorable, continue with 6.8.

6.7 Notify of approval

6.7.1 The ____ of GA will notify the applicant of its decision of approval of

premarket application three days after the evaluation meeting (Annex H).

6.8 Notify of non-approval

6.8.1 The ____ of GA will notify the applicant of its decision of non-approval of premarket application within three days of the evaluation meeting (Annex I).

6.8.2 The applicant may appeal the decision through the appeals procedure.

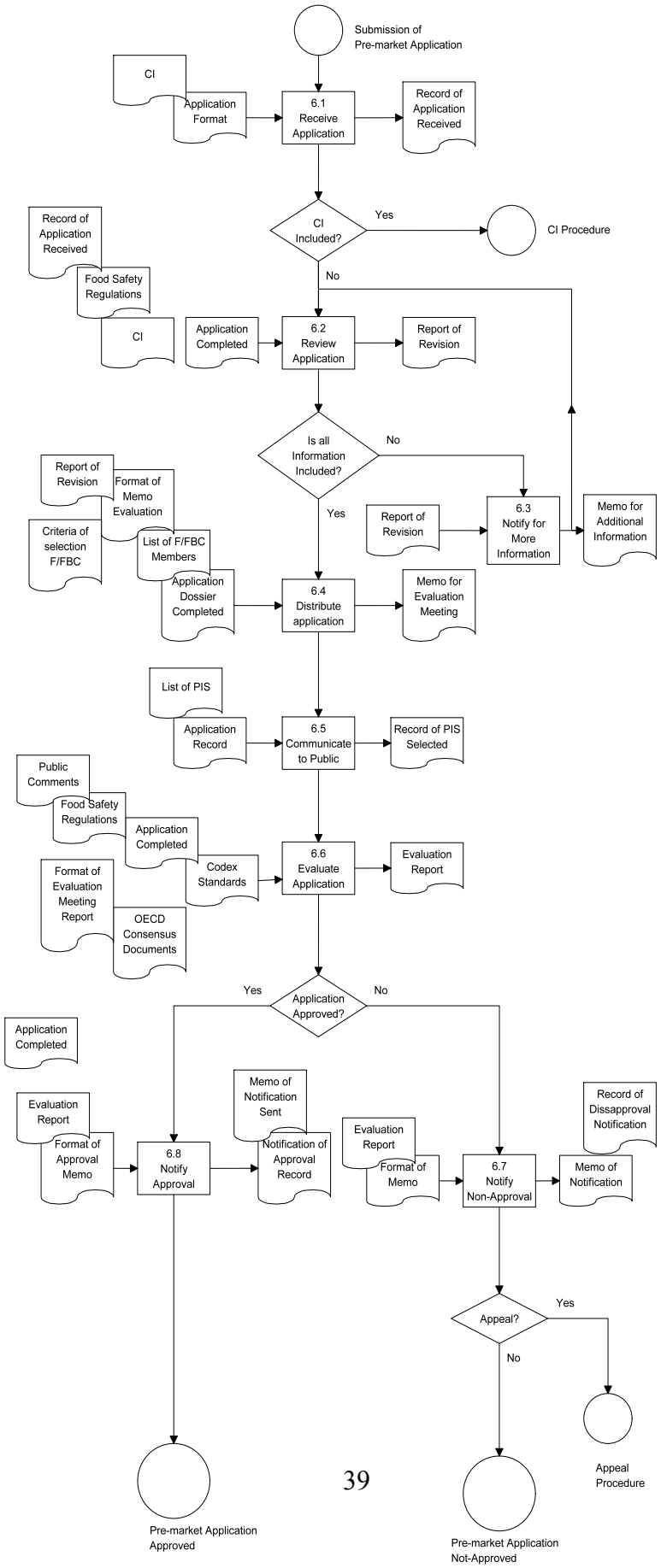
7 Records

7.1 Record of premarket application received
7.2 Record of FBC technical reports
7.3 Record of evaluation report
7.4 Note of approval premarket application
7.5 Note of non-approval premarket application
7.6 Record of PIS selected

8 Flowchart and Annexes

8.1 Flowchart
8.2 Annex A: Format: Premarket Application
8.3 Annex A.1: Format: Applicant Letter
8.4 Annex A.2: Consultation Information
8.5 Annex A.3: Information of Any Prior Evaluation (other agencies/countries)
8.6 Annex A.4: Data and Information of Method of Development
8.7 Annex A.5: Information About Substances Introduced/Modified in Food/Feed
8.8 Annex A.6: Comparable Food/Feed "Substantial Equivalence"
8.9 Annex A.7: Premarket Application
8.10 Annex B: Format: List of Premarket Applications received by GA
8.11 Annex C: Report of Revision Format
8.12 Annex D: Format: Memo requesting Additional Information
8.13 Annex E: Format: Criteria selection of Food/Feed Biosafety Experts
8.14 Annex F: Format: Memo of Evaluation Meeting
8.15 Annex G: Format: Technical Evaluation Report
8.16 Annex H: Format: Notification of Non- Approval Memo
8.17 Annex I: Format: Notification of Approval Memo
8.18 Annex J : Format: Public Communications
8.19 Annex K: Format: Record of PIS Selected

PRE-MARKET APPLICATION FOR FOOD/FEED DERIVED FROM BIOTECHNOLOGY PLANTS FLOWCHART



ANNEX A

Format: Premarket Application

- Applicant letter
- Consultation information
- Information on any prior evaluation (other agencies/countries)
- Data and information on method of development
- Information about substances introduced/modified in the food/feed
- Comparable food/feed “Substantial Equivalence”
- Premarket application form

Annex A.1
Format: Applicant Letter

Date:

To: Government Authority

From: Applicant (Name/Address/Tel/Fax/Email)

The food/feed derived from biotechnology plants included in this premarket application is as safe as comparable food/feed and the intended use is in compliance with all applicable requirements of the regulations. Included in this application is data and information demonstrating that this product, its ingredients or other derived products thereof are as safe as comparable products.

In the application we claim some CI and provide substantiation for each claim of CI. Each page containing CI is clearly marked as "Contains CI". If portions of a page are claimed to be CI this CI is enclosed within brackets ("[]").

_____
APPLICANT SIGNATURE

Annex A.2

Consultation Information

- Developer(s) name/address/tel/fax/Email
- Common and trade name of food/feed derived from biotechnology plants
- Consultation number
- Plant species from which food/feed is derived
- Distinctive designation of transformation event/unique identifier
- List of identity(ies) and source(s) of each introduced genetic material
- Description of the purpose or intended effect of the transformation event
- Information about the identity and function of expression products encoded by each introduced genetic material
- Information about estimated concentration of any expression product in the food/feed derived from biotechnology plants or products thereof
- Information about potential allergenicity and toxicity of expression products and the basis for considering safety
- Information comparing the nutritional and toxicological composition of the food/feed derived from biotechnology plants to its no transformed conventional counterpart
- Information regarding the potential for food/feed derived from biotechnology plants to induce an allergic response due to the genetic modification
- Description of the characteristic properties (physical, chemical, etc.) of food/feed derived from biotechnology plants
- Description of the intended applications or uses of food/feed derived from biotechnology plants
- Description of the expected changes in the food/feed composition
- Description of any application or use of food/feed derived from biotechnology plants that is not suitable
- Information on the plant or plant parts that will be consumed by animals

- Information on safe use in feed of the host plant and donor organism
- Description of potential adverse health effects to animals

Annex A.3

Information on Any Prior Evaluation
(Other agencies/countries)

- Name of the biotechnology food/feed and crop from which it is derived (OECD Unique Identifier)
- Agency name and contact person/Purpose of submission/ Result of Agency's Evaluation
- Copies of official documents from other countries
- Description of applications or uses of the biotechnology food/feed
- Information on the sources, identities and functions of introduced genetic material
- Information on the purpose or intended effect of the modification and its expected effect on the composition or properties of the food/feed
- Information on the comparison of the composition of the biotechnology food/feed with the food/feed derived from the parental variety in relation with important nutrients and toxicants that occur naturally in the food/feed
- Information on the identity and function of expression products encoded by the introduced genetic material
- Information regarding any known allergenicity and toxicity of expression products and the basis for concluding the safety human consumption
- Information on the potential for biotechnology food/feed to induce an allergic response has been altered by the genetic modification
- Any other information relevant to the safety and nutritional assessment of the biotechnology food/feed

ANNEX A.4

Data and Information on Method of Development

- Characterization of the host plant (including, but not limited to, scientific name, taxonomic classification, mode of reproduction, and pertinent history of development and use)

- Construction of the vector used in the transformation of the parent plant, with a thorough characterization of the genetic material intended for introduction into the parent plant and information regarding the transformation method, open reading frames, and regulatory sequences

- Characterization of each introduced genetic material, including the number of insertion sites, the number of gene copies inserted in each site, information on DNA organization within the inserts, and information on potential reading frames that could express unintended proteins in the transformed plant

- Data and other information related to the inheritance and genetic stability of each introduced genetic material

- Any other information considered relevant about the method of development

ANNEX A.5

Information about Substances Introduced/Modified in the Food/Feed

- Data and information about novel substances found in food/feed as a result of the genetic modification
- Data and information about the identity and function of these novel substances
- Information regarding dietary exposure to these substances
- A statement of the applicant's conclusion of the safe dietary exposure
- Information regarding the potential allergenecity of each novel substance
- Any other safety information associated with these substances (e.g., digestibility or toxicity for each novel substance)

Annex A.6

Comparable Food/Feed "Substantial Equivalence"

- Justification for selecting a specific food/feed as the comparable food/feed
- Information on historic uses of the comparable food/feed
- Data and information comparing the composition and characteristics of the food/feed derived from biotechnology plants to that of another commonly consumed food/feed
- Data and information about the changes in the level of naturally occurring nutrients, toxicants, and anti-nutrients
- Information on methods by which the modification to food/feed could be detected
- A narrative about the basis for the applicant's view that the food/feed derived from biotechnology is substantially equivalent to/as safe as the comparable food/feed

Annex A.7

Premarket Application

PREMARKET APPLICATION NUMBER: _____

1. GENERAL INFORMATION

- Applicant name/Address/ Tel/Fax/Email

2. DESCRIPTION OF THE HOST PLANT AND ITS USE AS FOOD/FEED

- Common/scientific names
- Taxonomic classification
- History of cultivation and breeding with the identification of traits that may adversely impact human health
- Information on the host plant's genotype/phenotype relevant to its safety, including any known toxicity or allergenicity
- History of safe use for consumption as food/feed
- Information on plant cultivation, transport, storage, processing.

3. DESCRIPTION OF THE PLANT DERIVED FROM BIOTECHNOLOGY

- Plant species
- Type/purpose of modification

4. DESCRIPTION OF THE DONOR ORGANISM(S)

- Common/scientific name
- Taxonomic classification
- History of safe use for consumption as food/feed
- Information on naturally occurring toxins, anti-nutrients, and allergens
- Information on past and present use

5. DESCRIPTION/CHARACTERIZATION OF THE GENETIC MODIFICATION

- Specific method used for the transformation
- Information on genetic determinants used (characterization, function, size, identity, copy number, location of the DNA sequence, expected function in the plant)
- Characterization/description of the inserted DNA sequences
- Number of insertion sites
- Copy number and sequence data of the inserted DNA sequences
- Identification of any open reading frames that could result in novel or fusion proteins
- Gene product(s)
- Function of gene product(s)

- Phenotypic description of the new trait(s)
- Level and site of expression of the gene product in the plant

6. SAFETY ASSESSMENT

6.1 Expressed Substances (Non-Nucleic Acid Substances)

- Assessment of possible toxicity: potential toxicity of expressed substances should be assessed on a case-by-case basis depending on the identity and biological function of the substance in the plant and the dietary exposure
- New substances can be conventional components of plant food, such as proteins, fats, carbohydrates, and vitamins, which are novel in the plant derived from biotechnology
- Identify the chemical nature and function of the newly expressed substance and identify the concentration of the substance including variations and mean values
- Evidence that the genes coding for known toxins or anti-nutrients present in the donor organisms are not transferred to the plant derived from biotechnology
- Information on amino acid sequence similarity between the protein and known protein toxins and anti-nutrients, as well as stability to heat or processing and to degradation in appropriate representative gastric and intestinal model systems
- An integrated, stepwise, case-by-case approach used in the assessment of the potential allergenicity of the newly expressed protein(s) should rely upon various criteria used in combination, and data should be obtained using scientific methods
- Amino acid sequence homology of the expressed protein(s) to known allergens

6.2 Compositional Analysis of Key Components

- Analyses of concentrations of key components of the plant derived from biotechnology and those typical of the food/feed should be compared with a conventional counterpart grown and harvested under the same conditions
- The number of trial sites should be sufficient to allow accurate assessment of compositional characteristics
- An adequate number of plants should be sampled and the methods of analysis should be sufficiently sensitive and specific to statistically detect variations in key components

6.3 Evaluation of Metabolites

- Safety assessment of the plants requires investigation of residue and metabolite levels in the food and assessment of any alterations in nutrient profile
- Where altered residue or metabolite levels are identified in foods, consideration should be given to the potential impacts on human/animal health using conventional procedures

6.4 Food Processing

- Information should be provided describing the processing conditions used in the production of ingredients obtained from the plant derived from biotechnology

6.5 Nutritional Modification

- Nutritional assessment should be performed to assess the consequences of the genetic insertions to existing nutrients
- Information should be provided about the expected intake of the food in relation with the nutritional implications of the altered nutrient profile at customary and maximum levels of consumption

6.6 Feed

- Evidence of degradation of novel protein
- Detection of "transgenic" DNA and protein in animal products
- Description of feed ingredients/nutrients, including information on processing and estimated feeding rates
- Data and information on the predicted amount of the novel feed in the complete diet.
- Estimation of dietary exposure
- Toxicology data and information
- Additional tests such as animal feeding in the case of bio-availability of nutrients
- Information/data about potential allergenic response in animals of endogenous allergens and the newly expressed proteins
- Results of laboratory animal studies and/or livestock feeding trials
- Appropriate test methodologies for the detection and identification of the new GE feed

ANNEX B

Format: List of Premarket Applications Received by GA
(Internal GA use)

Premarket number	Date received	Use: food, feed, both	Gene/gene product	Source of gene(s)	Intended effect	Designation of transformation event OECD Unique identifier	Applicant

ANNEX C

Report of Revision Format
(Internal GA use)

- Applicant letter
- Information about GE food/feed consultation
- Information about any prior evaluation from other agency or country
- Data and information on method of development
- Information about antibiotic resistance
- Information about substances introduced/modified
- Studies regarding the comparable food/feed substantial equivalence
- Description of the GE plant, host plant, its uses, the donor, and the genetic modification
- Results of the safety assessment regarding toxicity, nutritional modification, and allergenicity

ANNEX D

Format: Memo Requesting Additional Information

Premarket Application Number:

Date:

To: Applicant

From: GA

After an administrative revision of your application, the following information is deemed necessary to complete our assessment:

Example:

1) A description of the amount of gene product found at different phases of production and processing of the food/feed derived from biotechnology plants

2) Comparison of the amino acid sequence of the novel protein to other amino acid sequences of known allergens.

This information is required in order to continue evaluation of your application. Review of your application will be renewed upon receipt of the information required above.

_____

GA SIGNATURE

ANNEX E

Format: Criteria for Selection of Food/Feed Biosafety Experts

- Minimum five years professional experience in the field of competence related to the application
- Experience in risk assessment
- Attested scientific regard (provide list of relevant publications, awards)
- Ability to work with people of different cultural backgrounds
- Ability to work under short timelines
- A declaration of any interest which might be considered prejudicial to their independence
- A declaration of financial or other interest that may be reasonably appear to bias the outcome of the safety assessment

ANNEX F

Format: Memo Requesting Evaluation Meeting

Premarket Application Number:

Date:

To: Members of FBC

From: GA

I would like to convene a meeting of the FBC to evaluate premarket application #_____. Enclosed is a non-CI copy of the application. CI copies will be available at the meeting. In the event you require a CI copy to complete your review prior to the FBC meeting, these are available at the GA office during normal working hours. CI copies cannot be mailed.

The meeting will be held on --------- (fix date, time and place). On the event you cannot be present you may participate by teleconference @11-800-000000.

_____
GA SIGNATURE

Enclosure

ANNEX G

Format: Technical Evaluation Report

Premarket Application Number:

	COMPLETE/SUFFICIENT	
	YES	NO
Description of the GE		
Description of the host plant and its use as food		
Description of the donor organism		
Description of the genetic modification		
Characterization of the genetic modification		
Information on antibiotic resistance		
Assessment of toxicity		
Compositional analysis of key components		
Residues and metabolites in the bio-food		
Level of nutrients		
Assessment of allergenicity of food/feed		
Nutritional modification		
Food processing		
Food ingredients		
Food toxicity		
Assessment of substantial equivalence of food/feed		
Feed composition nutrients		
Feed ingredients		
Feed toxicity		

ANNEX H

Format: Notification of Non-Approval Memo

Premarket Application Number:

Date:

To: Applicant

From: GA

Your premarket application # _____ requesting an authorization to market the food/feed derived from biotechnology plants was declined. Attached is the respective technical report, which provides the reasons for declining.

You may appeal this decision in accordance with the regulations.

_____
GA SIGNATURE

ANNEX I

Format: Notification of Approval Memo

Premarket Application Number:

Date:

To: Applicant

From: GA

Your premarket application # _____ requesting an authorization to market the food/feed derived from biotechnology plants was approved. We have determined that your food/feed safety assessment supports the finding of safety for your product. Attached is the respective technical report, which may include conditions of approval.

_____
GA SIGNATURE

ANNEX J

Format: Public Communications

Premarket Application Number:

INFORMATION TO BE COMMUNICATED

Bio- food/feed	Gene/gene product	Host organism	Intended use	Designation (UI)	Applicant name	Date 1: Receipt 2: Final determination	PIS selected

ANNEX K

Format: Record of PIS Selected

Premarket application number	Public information system selected	Dates of publication	Comment period (# of days)	Number of comments received	Date of GA publication of determination	Copy of the publication YES NO

5. PROCEDURE FOR SCIENTIFIC EVALUATION FOR FOOD/FEED DERIVED FROM BIOTECHNOLOGY PLANTS

After meeting administrative requirements, the premarket application for food/feed derived from biotechnology will be evaluated for safety. If necessary, the GA will convene a meeting of the FBC to evaluate the safety of the food/feed derived from biotechnology. The scientific evaluation of food/feed derived from biotechnology includes consideration of substantial equivalence, safety of introduced genetic material and gene product, unintended effects, nutrition information, allergenicity, and toxicity concerns.

The substantial equivalence concept of the food/feed derived from the biotechnology involves a comparison with its conventional counterpart and will be one of the first safety comparisons conducted by the experts. In the application of this concept, the key components are considered on the basis of the history of safe use of the traditional counterpart; any differences between the biotechnology-derived food/feed and its traditional counterpart must be identified. The identified differences are then the subject of a safety assessment, which can include, but is not limited to, nutritional, toxicological and immunological testing as appropriate. A wide range of information is used in this comparison, such as key nutrients that may have a major impact on the total diet (including fats, proteins, carbohydrates, minerals, and vitamins) and recognized anti-quality components.

Depending on the result of the comparison, there could be a need for more extensive data or other designed studies to demonstrate food/feed safety. Afterwards, the GA or FBC will prepare a report of its substantial equivalence evaluation.

Another aspect that the GA or FBC must evaluate is the nutritional composition of the food/feed derived from biotechnology. This involves analysis of the concentrations of the key components of the bio-engineered food as they relate to human health. This analysis should also consider the extent to which the modified nutrient is bio-available and remains stable with time, processing, and storage. The expected intake of the modified product in food should be used to access the nutritional implications of the altered nutrient profile at customary and maximal levels of consumption. These results will provide some assurance that the potential of any undesirable nutritional effects will be detected.

In the case of feed derived from biotechnology plants, the GA or FBC will evaluate the nutritional data, such as nutrient and anti-nutrient composition and byproducts used in feed. In general, nutrient composition is related to protein, fat, fiber, lipids, carbohydrates, vitamins, and minerals. If the characterization of the feed indicates that the available data are sufficient for a thorough safety assessment, the GA will provide a report of the nutritional composition.

The next step in the evaluation is an assessment of the potential allergenicity of the food/feed derived from biotechnology plants. The extent of the allergenicity assessment will vary according to the nature of the source of the transferred genetic material. The potential for

allergenic response in humans or animals should be considered on the basis of the history of the host/parental and donor organisms and/or the novel traits introduced. A case-by-case determination should be applied in the assessment of possible allergenicity of the newly expressed proteins following the decision tree proposed by FAO/WHO.

The allergenicity assessment involves a comparison of the amino acid sequence of the introduced protein with known allergens as well as the stability of the introduced protein. In cases where the results of homology and stability studies lead to uncertainties regarding the potential for allergenicity, allergenicity-testing using recognized protocols should be considered. The GA or FBC will provide a report based on the results of the allergenic evaluation of the food/feed derived from biotechnology.

The extent of toxicological evaluation will be determined by the outcome of the assessment of the biological significance of any differences identified between the new food and its conventional counterpart. This evaluation will include studies on the newly expressed proteins, the consequences of any genetic modification, the presence of other novel constituents, and their possible changes. If identified, other novel constituents, such as metabolites, should be evaluated within toxicological tests.

Frequently, animals consume whole plants or part of them, so the nature of the genetic modification may be of relevance only to livestock feeding, as in the case of forages. In the case of forages derived from biotechnology plants, the GA would not conduct a food safety assessment. The novel protein may be absent or considerably concentrated, so this has implications for levels of exposure, choice of comparators, and for determining the concentration of the new protein used in acute/sub-chronic toxicity studies made with the novel protein. It is necessary to evaluate any novel protein in the frequency of use of the plant part or by-product, or the potential for disruption of the novel protein during any extraction or processing method. Acute limit dose tests using purified novel protein represents the minimally required toxicological study for toxicological evaluation. The results of this study and its assessment will guide the need for additional toxicity studies (such as metabolic and toxic kinetic results, sub-chronic oral and chronic toxicity) to be included in the toxicological evaluation. When the GA or FBC has finished the toxicity evaluation, they will issue a report of their findings.

Finally, GA or FBC will analyze the evaluation reports of each issue in order to determine the overall safety and to make a decision for approving or declining the marketing of food/feed derived from biotechnology.

The final step is to communicate to the public the result of the scientific evaluation and to provide an opportunity for public comment. The GA would take public comments into consideration and address these, if necessary, in the GA's assessment. This step gives more transparency to the GA safety assessment process.

SCIENTIFIC EVALUATION OF FOOD/FEED DERIVED FROM BIOTECHNOLOGY PLANTS PROCEDURE

GOVERNMENT AUTHORITY

Authorization Date	
Effective Date	
Created by	
Approved by	

1. Purpose

1.1 The objective of this procedure is to define the sequence of events, actions, interfaces, and responsibilities involved in the process of the scientific evaluation of a food/feed derived from biotechnology plants.

2. Scope

2.1 From receipt of a premarket application for a food/feed derived from biotechnology plants to the approval/disapproval for marketing

3. References

3.1 Premarket application approved
3.2 National Food Safety Regulations
3.3 Data, reports, other statistics
3.4 List of FBC members
3.5 WHO/FAO Guidelines
3.6 CODEX Standards
3.7 OECD Guidelines

4. Definitions

4.1 GE: Genetically Engineered
4.2 FBC: Food Biosafety Committee
4.3 CI: Confidential Information
4.4 GA: Government Authority
4.5 PIS: Public Information System.
4.6 OECD: Organization for Economic Cooperation and Development
4.7 WHO: World Health Organization
4.8 FAO: Food and Agriculture Organization
4.9 CODEX: Food Code Standards

5. Responsibility and Authority

5.1 If the GA determines that an FBC is required, the FBC will be responsible for evaluating the scientific, technical, and regulatory issues associated with the food/feed safety.
5.2 The ____ of GA is the agency responsible for distributing the premarket application approval.
5.3 The _____ of GA is responsible for convening the evaluation meeting of FBC.
5.4 The _____ of GA will take into consideration the public comments.
5.5 The _____ of GA is responsible for notifying the applicant about approval/disapproval of its application.
5.6 The ____ of GA is responsible for communicating to the public the bio-engineered food/feed approval/non-approval.

6. Activities

6.1 Distribute application

6.1.1 The ____ of GA will distribute the copies of the premarket application to the FBC through a memo (Annex A).
6.1.2 If the premarket application contains CI, go to CI Procedure.

6.2 Receive report
6.2.1 The ____ of GA will receive a report from the FBC by date established in Annex A.
6.2.2 The _____ of GA will record receipt of reports.

6.3 Convene FBC meeting
6.3.1 The _____ of GA will convene the scientific evaluation meeting through a memo to the FBC (Annex B).

6.4 Evaluate substantial equivalence
6.4.1 The FBC will evaluate the use history and equivalence of the food/feed derived from biotechnology plants comparing with its traditional counterparts, through a consideration of both intended and unintended effects.
6.4.2 The FBC will prepare a substantial equivalence report (Annex C).
6.4.2.1 If the food/feed derived from biotechnology plants is not considered a substantially equivalent, continue with 6.5.
6.4.2.2 If the food/feed derived from biotechnology plants is considered substantially equivalent, continue with 6.6.

6.5 Require additional information.
6.5.1 The _____ of GA may require additional information about the food/feed derived from biotechnology plants (Annex D).

6.6 Evaluate nutritional composition, allergenicity, and toxicity.
6.6.1 The FBC will evaluate the data and information on the application related to the nutrient composition, the biological efficacy of the nutrients in the food/feed, and the assessment of dietary intake and nutritional impact.
6.6.2 The FBC will evaluate the data and information on the premarket application related to the allergenic potential of the novel proteins.
6.6.3 The FBC will evaluate the data and information of the premarket application related to the allergenic potential of the novel proteins.
6.6.4 The FBC will prepare a report of the nutritional composition, allergenicity, and toxicity assessment (Annexes E, F, and G).

6.7 Communicate to public
6.7.1 The ____ of GA will communicate to the public the decision of the food/feed derived from biotechnology plants for marketing through the PIS selected, (Annex J).
6.7.2 The ____ of GA will maintain a record of the media notes (Annex K).

6.8 Evaluate food/feed safety

6.8.1 The FBC will evaluate the safety of the food/feed derived from biotechnology plants, taking into account all the reports in relation with the nutritional composition, allergenecity, and toxicity of the food/feed derived from biotechnology plants.

6.8.2 The FBC will prepare a final evaluation report about the food/feed safety (Annex H).

6.8.2.1 If premarket application is approved, continue with 6.9

6.8.2.2 If premarket application is not approved continue with 6.10

6.9 Notify of approval

6.9.1 The ____ of GA will notify the applicant through a memo that premarket application requested has been approved (Annex I) with or without conditions.

6.9.2 The ____ of GA will maintain a database of approved premarket applications. This database will be part of the information exchange mechanism Biosafety Clearing House established by the Cartagena Protocol on Biosafety.

6.10 Notify of non-approval

6.10.1 The ____ of GA will notify the applicant through a memo that the premarket application requested was not approved. (Annex I)

6.10.2 The applicant may appeal the decision within 90 working days after this notification following the Appeal Procedure.

6.10.2.1 If an appeal is received within the time limit, continue with the appeal procedure.

6.10.2.2 If an appeal is not received within the time limit, continue with 6.10 and the GA will close the record.

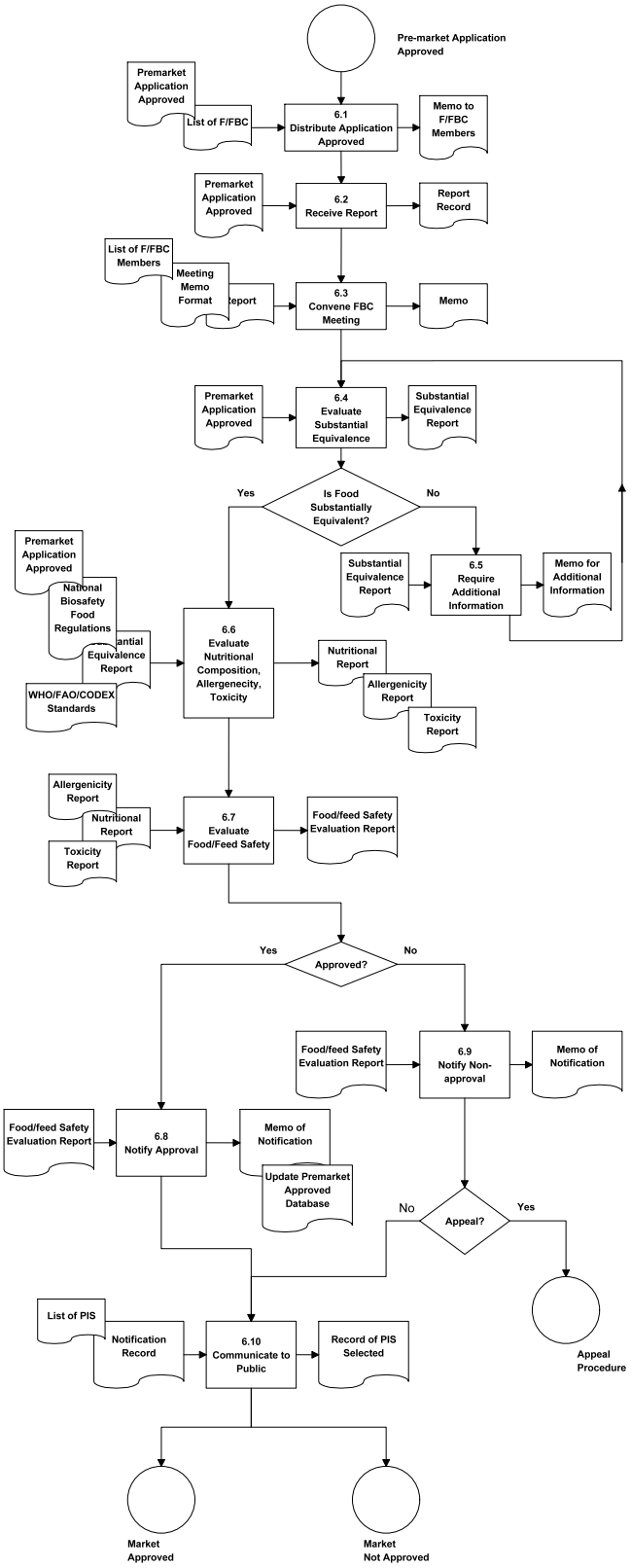
7. Records

7.1 Memo for application distribution and evaluation meeting to FBC
7.2 Substantial equivalence evaluation report
7.3 Memo for additional information
7.4 Nutritional evaluation report
7.5 Allergenicity evaluation report
7.6. Toxicity evaluation report
7.7 Food/feed safety final evaluation report
7.8 PIS contracted and copy of media notes
7.9 Note of the premarket application approval/non approval
7.10 Public communication on food/feed derived from biotechnology plants

8. Flowchart and Annexes

8.1 Flowchart
8.2 Annex A: Format: Distribution of Application to FBC
8.3 Annex B: Format: Memo Convening Meeting of FBC

SCIENTIFIC EVALUATION FOR FOOD/FEED DERIVED FROM BIOTECHNOLOGY PLANTS FLOWCHART



ANNEX A

Format: Distribution of Application to FBC

Premarket Application Number:

Date:

To: FBC Members

From: GA

With reference to Premarket Application # _____ requesting permission to market, attached is a non-CI copy of this application.

I would be grateful if you would send me your technical report in the next 45 working days.

If you require any further information necessary to reach a determination of safety, please indicate the nature of the information as early as possible. A compiled list of the information required by each of the FBC members will be forwarded to the applicant.

We will notify you of the date, time, and location of when the FBC for Premarket Application #_____ will convene.

_____
GA SIGNATURE

ANNEX B

Format: Memo Convening Meeting of FBC

Premarket Application Number:

Date:

To: FBC Members

From: GA

You are hereby convened to participate on DD/MM/YY at 00:00h hrs to evaluate the Premarket Application # _____. This meeting will take place at _____ (address). The evaluation of this application will be made in the form of a final report to the GA.

If you are unable to be present, please mail or fax your written comments by DD/MM/YY. You may all participate by teleconference @ 1-800-00000.

_____
GA SIGNATURE

ANNEX C

Format: Substantial Equivalence Evaluation Report

Premarket Application Number:

Date:

In comparing the food/feed derived from biotechnology plants with its conventional counterpart with respect to agronomic data and compositional data on key nutrients and toxicants, our conclusion is as follows (choose one):

- The food/feed derived from biotechnology plant products is substantially equivalent to its conventional counterpart;

- The food/feed derived from biotechnology plant products is substantially equivalent to its conventional counterpart, except for a few clearly defined differences; or

- The food/feed derived from biotechnology plant products is not substantially equivalent to its conventional counterpart either because biologically relevant differences have been identified or because there is no existing counterpart to compare it with.

MEMBERS OF FBC

ANNEX D

Format: Memo to Applicant Requesting Additional Information

Premarket Application Number:

Date:

To: Applicant

From: GA

After evaluation of your premarket application, the following information is required in order to continue with this Agency's evaluation:

_____

_____

_____

If you claim any of the requested information as confidential, please provide a justification for each claim made.

Further review of your application will be placed on hold until the requested information is provided.

_____

GA SIGNATURE

ANNEX E

Format: Nutritional Composition Evaluation Report

Premarket Application Number:

Date:

1. Composition of food:

2, Dietary importance of the food:

3. Bioavailability of:

    - Nutrients
    - Protein
    - Lipids
    - Carbohydrates
    - Vitamins
    - Minerals

4. Feed nutrient composition:

    - Crude protein
    - Crude fat
    - Fibre: crude fibre, acid, or neutral detergent fibre
    - Lipids
    - Carbohydrate fraction
    - Vitamins
    - Minerals

5. Dietary exposure

ANNEX F

Format: Allergenicity Evaluation Report

Premarket Application Number:

Date:

Source of the genetic material

- Commonly allergenic
- Rarely allergenic
- Unknown allergenic potential

Sequence homology of the novel protein

- Comparison of the amino-acid sequence to known allergens

Stability of the introduced protein

- Simulated mammalian gastric digestion system
- Process stability of the introduce protein (effects of pH, temperature, and other relevant conditions of processing)
- Digestive stability assessments

Immunochemical Reactivity with IgE antibodies (if warranted)

- Immune-assays
- In-vivo skin-prick test

ANNEX G

Format: Toxicity Evaluation Report

Premarket Application Number:

Date:

- New substances in the plant derived from biotechnology (proteins, fats, carbohydrates, vitamins)
- New metabolites from the activity of the novel substances
- Chemical nature and function of the novel substances
- Concentration with variation and mean values
- Current dietary exposure and possible effects on population sub-groups
- Identification of known toxins present in donor organism
- If it is not a preexisting substance used in feed, studies of metabolism, toxic kinetic, acute oral, sub chronic and chronic toxicity, reproduction, and development may be required

ANNEX H

Format: Food/Feed Safety Final Evaluation Report

Premarket Application Number:

Date:

From: FBC

To: GA

In accordance with the data and information provided in Premarket Application #_____, the food/feed has been determined to be: (mark one)

_____ **AS SAFE**
_____**NOT AS SAFE**

As the comparable counterpart; and pursuant to all applicable requirements of the regulations, it **MAY/ MAY NOT** be marketed.

_____
FBC SIGNATURE

ANNEX I

Format: Approval/Non-Approval Notification

Premarket Application Number:

Date:

To: Applicant

From: GA

Your Premarket Application # _____ requesting safety assessment of a food/feed derived from a biotechnology plants **HAS BEEN/ HAS NOT BEEN** approved for marketing. Attached is the respective technical report which provides the reasons for approval/non-approval.

If the application is APPROVED WITH CONDITIONS or NOT APPROVED, you may appeal the decision in accordance with the regulations and following the appeal procedure.

_____
GA SIGNATURE

Enclosure

ANNEX J

Format: Public Communication of GA Determination

Premarket Application #	Applicant Name	Food/ Feed	Gene/Gene Product	Host Organism	Intended Effect	STATUS				
						Approved MM/DD/YY	Approved with conditions MM/DD/YY	Withdrawn MM/DD/YY	Amended MM/DD/YY	Denied MM/DD/ YY

ANNEX K

Format: Record of PIS Selected

PREMARKET APPLICATION #	PUBLICATION SITE(S)	DATE(S) OF PUBLICATION	COPY OF THE PUBLICATION(S)

6. PROCEDURE FOR APPEAL

When a request to introduce a food/feed derived from biotechnology plants into the market has been denied or conditions have been imposed, the applicant has the right to appeal the GA's decision through an appeal procedure.

The GA is responsible for receiving the request to appeal, reviewing the observations and supporting documentation presented by the applicant, and convening a meeting of all parties. The GA will designate an appeal panel comprised of experts from the public and private sector.

The GA will prepare a preliminary report, taking into account all relevant information, and will arrange a meeting between the appeal panel and the appellant.

The purpose of the meeting is to give the appellant an opportunity to present and debate the merits of his/her appeal. Based on the evaluation and outcome of the meeting, the appeal panel will report its decision and prepare a report for the GA. The appeal panel can conclude that the GA's decision should be upheld, reversed, or reversed with conditions.

If the GA's decision is reversed, the GA will notify the appellant that his/her appeal has been accepted; therefore, the permission for premarket of a food/feed derived from biotechnology plants is approved.

If the GA's decision is upheld, the GA's legal department must review the decision report based on legal aspects to ensure compliance with all legal processes, then the GA will notify the appellant of the disapproval of the premarket for food/feed derived from biotechnology plants.

APPEALS PROCEDURE

GOVERNMENT AUTHORITY

Authorization Date	
Effective Date	
Created by	
Approved by	

1. Purpose

1.1 The objective of this procedure is to define the procedures to be followed to appeal a decision taken by the GA

2. Scope

2.1 From receipt of the applicant's request to appeal to the report of the final decision.

3. References

3.1 Food biosafety regulations, standards

3.2 Legal procedures

4. Definitions

4.1 GA: Government Authority

4.2 FBC: Food Biosafety Committee

4.3 AP: Appeal Panel

5. Responsibility and Authority

5.1 The ____ of GA is responsible of receiving the appeal, establishing the date to meet with the FBC, and obtaining reports and previous documents.

5.2 The FBC is responsible for publishing a preliminary report after the meeting.

5.3 The ____ of GA and its legal department are responsible for making a decision, which will be considered definitive.

6. Activities

6.1. Receive appeal

6.1.2 The ____ of GA will receive and record the appeal request within the allowable time limit (30 days after notification) (Annex A).

6.2 Review appeal

6.2.1 The _____ of GA will review the appeal request and make a preliminary report within a period of 30 working days.

6.2.2 The _____ of GA will schedule a date to have a meeting with the FBC and the applicant.

6.3 Meeting with the appellant

6.3.1 The _____ of GA will coordinate the meeting with the appeal panel and the appellant (Annex B).

6.4 Review decision

6.4.1 After the meeting, the ____ of GA will make a decision within five working days.

6.4.1.1 If the decision is favorable, the premarket application for food/feed derived from biotechnology will be approved.
6.4.1.2 If the decision upholds the GA's decision, continue with 6.5.

6.5 Review by the legal department
6.5.1 The legal department of GA will review the appeal, the preliminary report, and the decision report and will report its conclusions.

6.6 Notify the appellant
6.6.1 The ____ of GA with the legal report and the decision report will notify the appellant of the definitive decision.

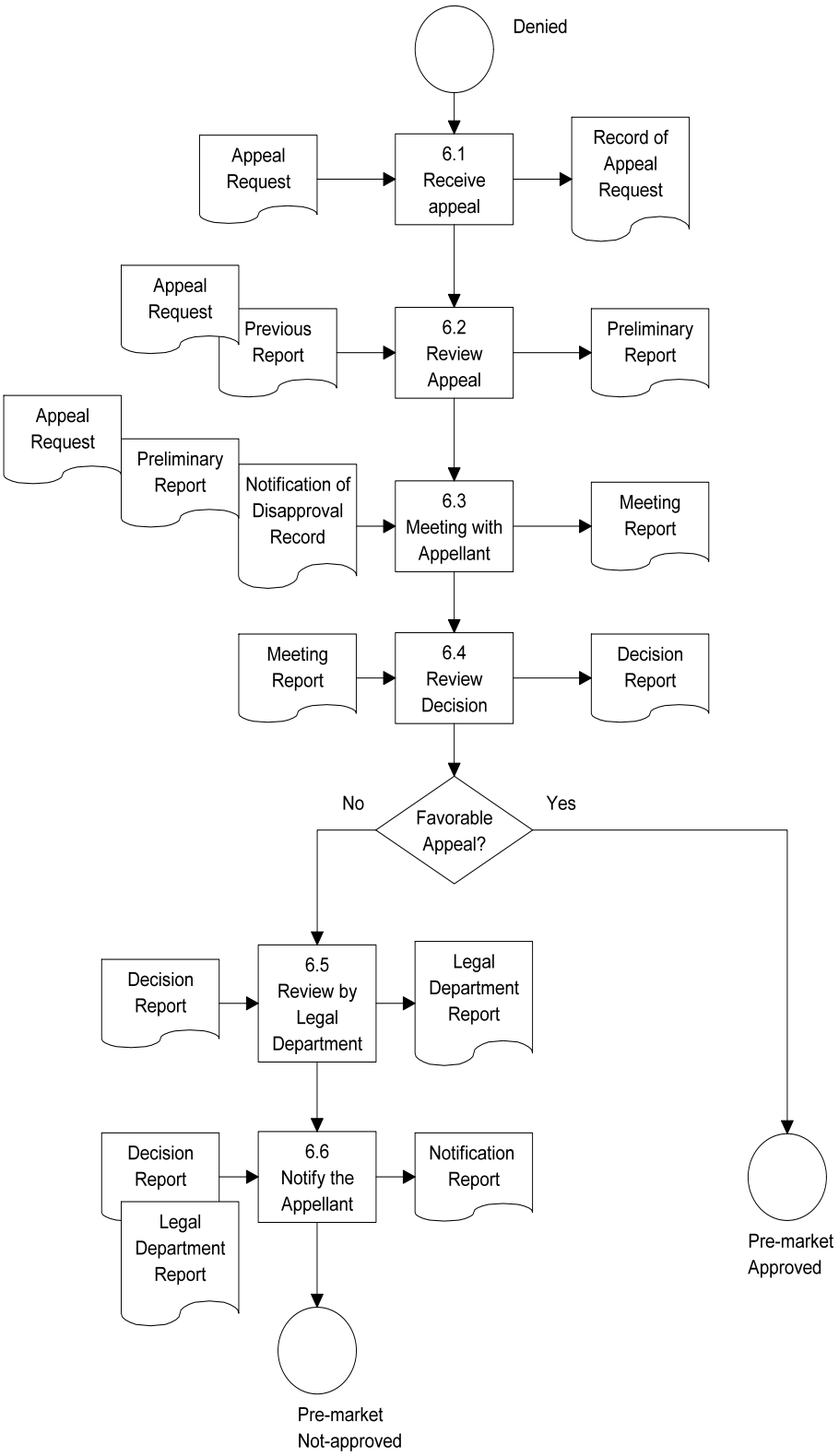
7. Records

7.1 Record of appeal request
7.2 Preliminary report
7.3 AP meeting report
7.4 Decision report
7.5 Report of the legal department
7.6 Notification report

8. Flowchart and Annexes

8.1 Flowchart
8.2 Annex A: Format: Memo Request for Appeal
8.3 Annex B: Format: Memo for Appeal Meeting

APPEALS PROCEDURE FLOWCHART



ANNEX A

Format: Memo Request for Appeal

Premarket Application Number:

Date:

To: GA

From: Applicant

As per your letter of DD-MM-YY in which you notify us that our application # _____ was denied, I hereby wish to exercise my right to appeal this decision and/or the conditions of approval.

In accordance with your procedures, I am filing this appeal within the established time limits and annexing pertinent additional information.

_____
APPLICANT SIGNATURE

ANNEX B

Format: Memo for Appeal Meeting

Premarket Application Number:

Date:

To: Applicant and FBC Experts

From: Government Authority

I hereby notify you that your participation is required in the appeal meeting that will be held on _____ (MM/DD/YY), in _____ (address), at _____ (time).

During this meeting, we will discuss the technical aspects presented in the applicant's appeal.
If you are not being able to be present, you may call into the meeting at 1-800-0000.

_____
GA SIGNATURE

7. DOCUMENT CONTROL PROCEDURE

All the documents and data shall be established and maintain following a document control procedure under the responsibility of the GA who shall review and approve them prior to issue.

Documents and data can be in the form of any type of media, such as hard copy or electronic. A master list shall be established to identify the status of the documents and data. Any changes to documents and data shall be reviewed and approved by the authority and shall be distributed to the concerned personnel.

This document control procedure shall ensure that appropriate documents are available, invalid or obsolete documents are removed, and obsolete documents are identified.

DOCUMENT CONTROL PROCEDURE

GOVERNMENT AUTHORITY

Authorization Date	
Effective Date	
Created by	
Approved by	

1. Purpose

1.1 Identify events, actions, activities and responsibilities involved in the creation, identification, approval, distribution, and storage of controlled documents.

2. Scope

2.1 From the document and data identification to the implementation of their control. This will be applied to documents related to the safety assessment of food/feed derived from biotechnology plants.

3. References

3.1 Model for Document Generation

4. Definitions

4.1 Document: Procedures, work instructions, references, specifications, or regulatory material for the administration of the system.

4.2 Data: Quantified information in documents.

4.3 Controlled document: Documents formally identified. These documents are registered, maintained and their change, as well as, their implementation is regulated.

4.4 Procedure: Document that describes, "Who does the job," "when," "where," and "why."

4.5 Work instructions: Document that identifies the procedures to perform a task or activity.

4.6 Internal document: Document generated outside the limits of the administrative system. For example, a regulatory document that is referred to a procedure or work instruction.

4.7 Master list: List that contains information related to documents and includes information such as document titles, revision numbers, and document codes.

5. Responsibility and Authority

5.1 The _____ of GA will assure that document control is conducted following this procedure, as described below in section 6, Activities.

6. Activities

6.1 Identify Documents

6.1.1 Any representative of the GA that needs a new controlled document will inform the GA, who will determine whether or not to proceed with the request and create the master list of controlled documents.

6.2 Create documents

6.2.1 If the document does not exist, the GA will assure that this document is created. The procedures and work instruction will be

prepared following the model approved by GA.

6.3 Review document

6.3.1 If the document already exists, the GA will review it to assure that the information is current and achieves the needs of the system, and that it is on the document master list. If the document is not adequate, the GA will modify the internal document according activity 6.5

6.3.2 The ____ of GA, before their approval, will review the new documents.

6.4 Approve document

6.4.1 Changes in the procedures won't be allowed, except for those related to work instructions and identification of responsibilities.

6.4.2 The ____ of GA will review and approve the new document to verify its precision.

6.5 Request document change

6.5.1 Any representative of the GA can request any change to the documents through the Document Change Application. The GA will evaluate the application, as well as its consequences, and will either authorize it or not authorize it.

6.5.2 The modified document will be controlled through activity 6.6.

6.6 Control documents

6.6.1 The _____ of GA will assure that the following conditions are met.

6.6.1.1 The master list of controlled documents is kept in both hardcopy and electronically.

6.6.1.2 The controlled documents are available and identified in the master list.

6.6.1.3 These documents are stamped as "controlled document."

6.6.1.4 In the case that the elements of the system are kept electronically (in red), the obsolete documents will be identified and removed to prevent use.

6.6.1.5 Confidential documents will be identified with stamp and will only be available to authorized personnel who will be identified in the work instructions.

6.6.2 Obsolete documents

6.6.2.1 The GA will EITHER DESTROY the obsolete documents or file them. The word "OBSOLETE" will be stamped on the cover page or diskette, and they will be filed in the section of obsolete documents. OBSOLETE documents will be

destroyed six months after being stamped “OBSOLETE.”

6.6.3 Photocopies

6.6.3.1 Photocopies and printouts of controlled documents will be made only for internal training and revisions. Photocopies of confidential documents are not allowed under any circumstance.

6.7 Distribute Documents

6.7.1 The ____ of GA will determine a date for the document to become valid.

6.7.2 The _____ of GA will distribute the new document.

6.8 Inform the concerned personnel and institutions

6.8.1 The _____ of GA will assure that the concerned personnel understand the content of the new document or any change made to the original document.

6.8.2 The _____ of GA will provide the training to the personnel as needed to achieve the new requirements.

6.9 Ensure access

6.9.1 The _____ of GA will ensure that documents of reference are available.

7. Records

7.1 Master list of controlled documents

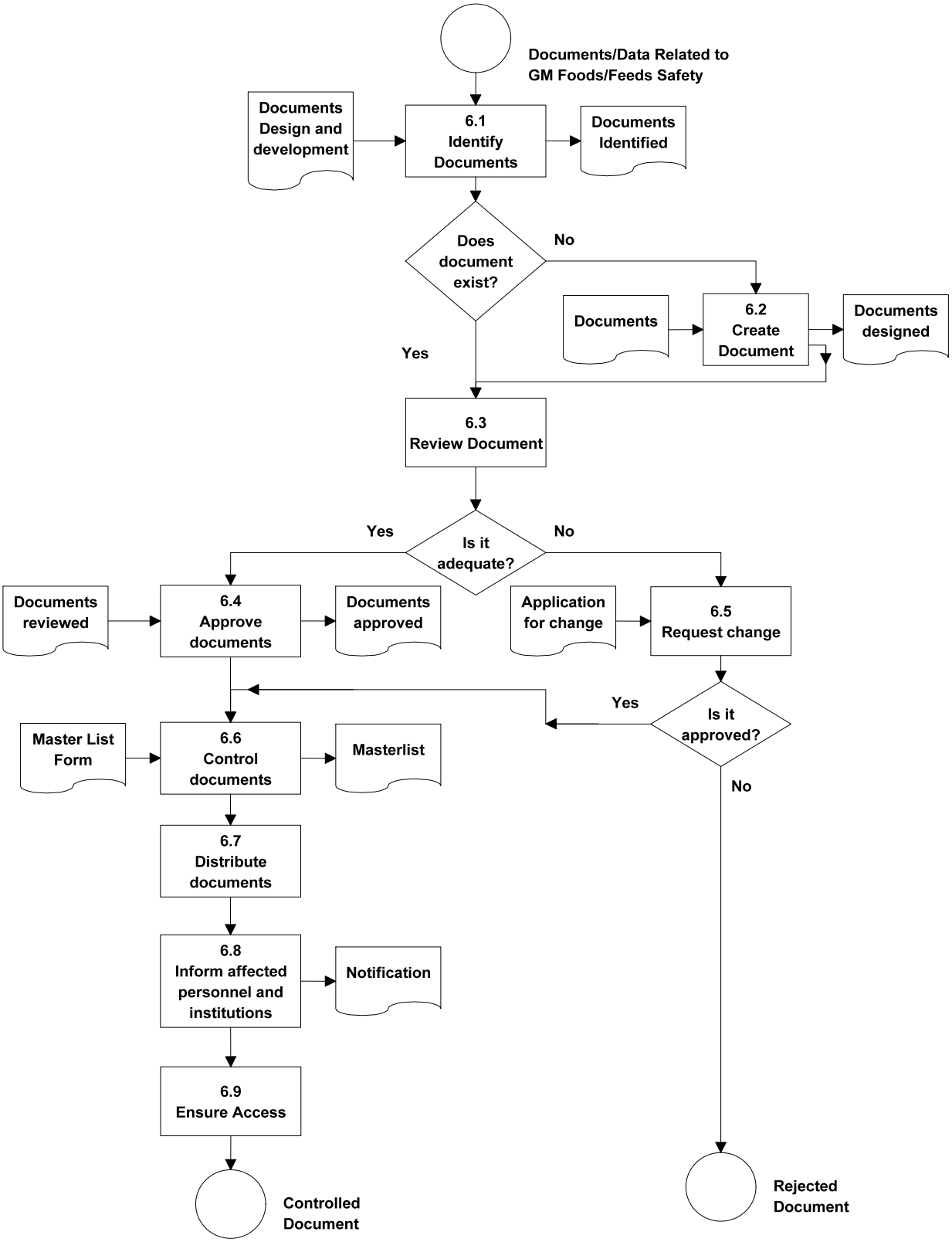
8. Flowchart and Annexes

8.1 Flowchart

8.2 Annex A: Controlled Documents Master List

8.3 Annex B: Document Change Application

FLOWCHART: DOCUMENT CONTROL PROCEDURE



ANNEX A

Controlled Documents Master List

DOCUMENT	TITLE	NUMBER OF CODE	REVISION *	PERSON NAME OR LOCATION	COMMENTS

* If the document does not have a revision, utilize the date as an identifier

ANNEX B

Format: Document Change Application

<table>
<tr><td colspan="2">CHANGE REQUESTED BY</td><td>APPLICATION DATE:</td></tr>
<tr><td colspan="3">DOCUMENT TITLE</td></tr>
<tr><td colspan="3">CHANGE REQUESTED</td></tr>
<tr><td colspan="3">REASON</td></tr>
<tr><td colspan="3">RECOMMENDATION (SELECT ONE)</td></tr>
<tr><td colspan="3">€ REJECT (reason)</td></tr>
<tr><td colspan="3">€ ACCEPT WITH CHANGES (explain)</td></tr>
<tr><td colspan="3">€ ACCEPT</td></tr>
<tr><td>IF ACCEPTED</td><td>SUGGESTED DATE</td><td>VALID SINCE</td></tr>
<tr><td colspan="3">TRAINING</td></tr>
<tr><td colspan="2">RECEIVED BY COORDINATOR OF DOCUMENT CONTROL</td><td>DATE</td></tr>
<tr><td colspan="2">AUTHORIZATION</td><td>DATE</td></tr>
</table>

8. RECORD CONTROL PROCEDURE

The GA shall establish a documented procedure for identification, collection, filling, access, storage, maintenance and discharge of records.

Records shall be maintained to demonstrate conformance to requirements and the effective evidence of the specific activity.

All records shall be stored and retained in such a way to prevent loss and to be available for evaluation during an audit or traceability. Records may be in the form of any type of media, such as hard copy or electronic.

RECORD CONTROL PROCEDURE

GOVERNMENT AUTHORITY

Authorization Date	
Effective Date	
Created by	
Approved by	

1. Purpose

1.1 The objective of this procedure is to define the events, actions, interfaces, and responsibilities involved in the identification, collection, file, access, storage, maintenance, and discharge of records.

2. Scope

2.1 From records that have been generated through the procedures of the safety assessment of food and/or feed derived from biotechnology plants to their control.

3. References

3.1 Administrative, Operational and Support Procedures
3.2 Regulations of Public Administration
3.3 Master List of Records

4. Definitions

4.1 Record: Document (electronic or print), product, or sample statement which will confirm that a procedure (or part of the procedure) has been carried out.
4.2 Controlled record: a record that is required to be kept and maintained under safeguard for future references.

5. Responsibility and Authority

5.1 The ____ of GA is responsible for identifying, collecting, filing, storing, discharging, and destroying records.

6. Activities

6.1 Identify records

6.1.2 The ____ of GA will identify the records to be controlled, as indicated by Administrative, Operational and Support Procedures and the Public Administration Regulation, and these records will be included in the master list of records.

6.2 Control records

6.2.1 The ____ of GA will collect, file, and keep the records.
6.2.2 The ____ of GA will control access to the records.

6.3 Dispose of records

6.3.1 The ____ of GA will periodically evaluate the master list of records and will dispose of obsolete records.

6.4 Review records

6.4.1 The _____ of GA will prepare a record review schedule with the purpose of verifying if the records are created and maintained in an

adequate manner.

7. Records

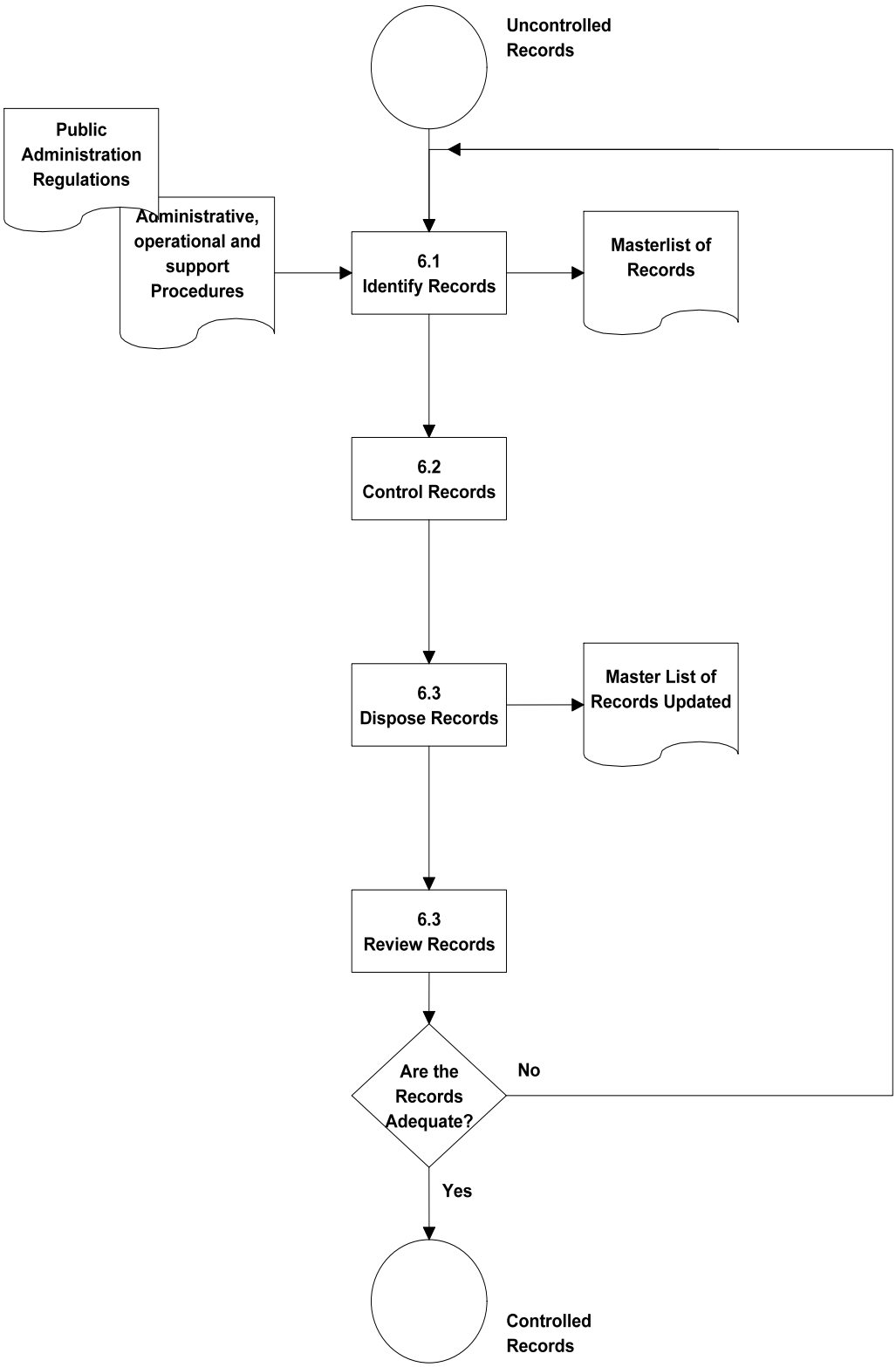
7.1 Master List of Records

8. Flowchart and Annex

8.1 Flowchart

8.2 Annex A: Master List of Records

FLOWCHART: RECORD CONTROL PROCEDURE



ANNEX A

Format: Master List of Records

RECORD TITLE	CODE NUMBER	PERIOD OF RETENTION	DATE OF DISPOSAL	DISPOSAL AUTHORIZED BY	DISPOSAL MADE BY	METHOD OF DISPOSAL	COMMENTS

9. REFERENCES

Canadian Food Inspection Agency, 2003, "Draft Guidelines for the safety Assessment of Novel Feed from Plant Sources".

Canada Health GM Foods and other Novel Foods, www.hc-sc.gc.ca/fn-an/gmf

Center for Food Safety and Applied Nutrition, Office of Food Additive Safety, 2004, "Draft Guidance: Recommendations for the Early Food Safety Evaluation of New Non-Pesticide Proteins produced by New Plant Varieties Intended for Food Use".

European Commission, Health and Consumer Protection Directorate General, 2003, "Guidance Document for the Risk Assessment of Genetically Modified Plants and derived Food and Feed".

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10. GLOSSARY OF TERMS

Adverse effect: Change in morphology, physiology, growth, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences.

Allele: a variant form of a gene. In a diploid cell there are two alleles of every gene (one inherited from each parent, although they could be identical). Within a population there may be many alleles of a gene. In heterozygote with co-dominant alleles, both are expressed.

Allergen: A substance that causes an immune response (allergic reaction). Antigenic substance capable of producing immediate hypersensitivity.

Allergy: A hypersensitivity (characterized by a damaging immune response) to an allergen or substance in a person's environment such as dust, pollen, fur or a chemical Can manifest as high fever, skin rash, asthma, food allergies etc.

Amino Acid: the constituent subunit of proteins. A group of compounds that make up the building blocks of proteins.

Animal: for the purposes of this Manual animal includes all mammals and non-mammals.

Antibiotic: A class of natural or synthetic compounds that inhibit the growth of, or kill some microorganisms. Antibiotics are widely used medicinally to control bacterial pathogens. Resistance to antibiotics may develop through mutations and selection of these mutations.

Antibiotic resistance: The ability of a microorganism to disable an antibiotic or prevent its transport into the cell.

Antibody: A protein produced by the immune system in response to an antigen (a molecule that is perceived to be foreign). Antibodies bind specifically to their target antigen to help the immune system render the foreign entity harmless.

Anti-nutrients: Substances that act in direct competition with or otherwise inhibit or interfere with the use or absorption of a nutrient.

Assay: 1. Test or evaluation. 2. The procedure for measuring the quantity of a given substance in a sample (chemically or by other means).

Bioavailability: The proportion of a nutrient or administered drug etc. that can be taken up by an organism in a biologically effective form. For example, some soils high in phosphorus (P) have a low level of P availability because the pH of the soil renders much of the P insoluble.

Biocatalysis: The use of enzymes to improve the efficiency of chemical reactions.

Biosynthesis: Formation of a chemical compound by a living organism.

Biotechnology: 1. "Any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use" (Convention on Biological Diversity). 2. " Interpreted in a narrow sense, a range of different molecular technologies such as gene manipulation and gene transfer, **DNA** typing and cloning of plants and animals."

Biosafety: Referring to the avoidance of risk to human health and safety, and to the conservation of the environment, as a result of the use for research and commerce of infectious or genetically modified organisms.

Biological containment: Restricting the movement of organisms. Can take two forms: making the organism unable to survive in the outside environment, or making the outside environment inhospitable to the organism. For microorganisms, the favored approach is to engineer organisms to require a supply of a specific nutrient that is usually available only in the laboratory. For higher organisms (plants and animals), restricting movement is done by limiting the organism to grow, spread, and/or reproduce.

Carbohydrate: (polysaccharide) a linear or branched polymer (e.g. starch, cellulose, etc.) composed of covalently linked monosaccharide, including cellulose, pectin and starch.

Cloning Vector: a small, self-replicating DNA molecule usually a plasmid or viral DNA chromosome into which foreign DNA is inserted in the process of cloning genes or other DNA sequences of interest. It can carry inserted DNA and be perpetuated in a host cell.

Codex Alimentarius Commission: An international regulatory body (jointly administered by FAO and WHO) responsible for the definition of a set of international food standards. The Commission periodically determines, then publishes a list of food ingredients and maximum allowable levels (the *Codex Alimentarius*) deemed to be safe for human consumption. Codex standards are voluntary though most countries adopt them into national law.

Composition Analysis: The determination of the concentration of compounds in a plant or animal tissue. Compounds that are commonly quantified are proteins, fats, carbohydrates, minerals, vitamins, amino acids, fatty acids and anti-nutrients.

Confidential Information: Information deemed by the applicant to have biosafety, business, commercial, trade, or other value which needs to be protected and if divulged may result in economic or commercial injury.

Consultation: necessary discussion/interaction with the authority.

Containment: Physical and temporal measures applied to limit spread of organisms into the external environment. *Synonym*: contained use. Any operation, undertaken within a facility, installation or other physical structure, which involves living modified organisms that are controlled by specific measures that effectively limit their contact with and their impact on, the external environment.

Contaminant: 1. an undesired biological or chemical entity present in a compound or mixture of compounds. 2. Any micro-organism accidentally introduced into a culture or culture medium. The contaminant may compete with the desired cells and consequently inhibit their growth, or totally replace them. Synonym: Antecedent parent, untransformed line

Conventional Counterpart: means a related plant variety, its components and/or products for which there is experience of establishing safety based on common use as food.

Co-transformation: A protocol for producing transgenesis, in which host (plant or animal) cells are transformed simultaneously with two different plasmids, one of which carries a selectable marker, and the other the gene to be transferred. Relies on the observation that given a sufficiently high concentration of both plasmids, transformed cells will have incorporated both plasmids. If the transgenes are separable through normal meiotic recombination, transgenic individuals without the selectable marker can be selected in subsequent generations.

Chronic Toxicity: 1. adverse effects following chronic exposure. 2. Effects which persist over a long period of time whether or not they occur immediately upon exposure or are delayed.

Chromosome: In eukaryotic cells, chromosomes are the nuclear bodies containing most of the genes largely responsible for the differentiation and activity of the cell. Chromosomes are most easily studied in their contracted state, which occurs around the metaphase of mitosis or meiosis; they contain most of the cell's DNA in the form of chromatin. Each eukaryotic species has a characteristic number of chromosomes. Bacterial and viral cells contain only one chromosome, which consists of a single or double strand of DNA or, in some viruses, RNA

Dehydrogenase: An enzyme that catalyses the removal of hydrogen atoms in biological reactions.

Dehydrogenation: A chemical reaction in which hydrogen is removed from a compound.

Deoxyribonucleic Acid (DNA): Large molecule found in the cells of all organisms. It carries the information that allows organisms to function, repair and reproduce themselves.

Diagnostic Procedure: A test or assay used to determine the presence of a specific substance such as an organism, specific nucleic acid sequence, protein, or other macromolecules.

Diet: A specific allowance or selection of food or feed that a person or animal regularly consumes.

Dietary exposure: The quantity or fraction of a product in a food or food item which is actually consumed.

DNA: (deoxyribonucleic acid) the molecule that encodes genetic information.

DNA Sequencing: Technologies through which the order of base pairs in a DNA molecule are determined.

Donor: the organism from which genetic material is derived for insertion into another organism.

Dose- Response Assessment: the determination of the relationship between the magnitude of exposure (dose) of a chemical, biological or physical agent to the severity and/or frequency of an associated health effect (response).

ELISA: abbreviation for enzyme linked inmunosorbent assay. An immune-assay, i.e. an antibody based- technique for the diagnosis of the presence and quantity of specific molecules in a mixed sample. It combines the specificity of an immunoglobulin with the detect ability of an enzyme generated colored product. In one form the primary antibody is adsorbed into a solid substrate, and a known amount of the sample is added; all the antigen in the sample is bound by the antibody. A second antibody specific for a second site on the test of protein is added; and the enzyme generates a color change in the presence of a substrate reagent.

Enterotoxin: A bacterial protein that, following release into the intestine, causes cramps, diarrhea and nausea.

Enzyme: A biological catalyst:. A protein which, in very low concentration, catalyses specific chemical reactions but is not used up in the reaction. Enzymes are classified into six major groups (1-6), according to the type of reaction they catalyze: 1. oxidoreductases; 2. transferases; 3. hydrolases; 4. lyases; 5. isomerizes; 6. ligases.

Enzyme immunoassay: A range of immunoassay techniques employing enzymes, which includes **ELISA**.

Enzyme kinetics: The quantitative characteristics of enzyme reactions.

Enzyme stabilization: Maintaining the active conformation of an enzyme. This can be achieved *in vitro* by providing the appropriate chemical environment and cofactors. In some cases binding an antibody to the enzyme, in such a way that the active site of the enzyme is left unblocked, can reduce the criticality of these factors.

Eukaryote: One of the two major evolutionary clades (the other being prokaryote), characterized by having the nucleus enclosed by a membrane, and possessing chromosomes that undergo mitosis and meiosis. Eukaryotic organisms include animals, plants, fungi and some algae.

Event: A selected particular insertion site of a transgene based on agronomic performance, expression pattern or other criteria. A term used to describe a plant and its offspring that contain a specific insertion of DNA. Events are distinguishable from each other by their unique site of integration of the introduced DNA.

Exposure: 1. Concentration, amount or intensity of a particular physical or chemical agent or environmental agent that reaches the target population, organism, organ, tissue or cell, usually expressed in numerical terms of substance concentration, duration, and frequency (for chemical agents and micro-organisms) or intensity (for physical agents such as radiation). 2. Process by which a substance becomes available for absorption by the target population, organism, organ, tissue or cell, by any route.

Expression system: Combination of host and expression vector which provides a genetic context for making a cloned gene functional, i.e. produce peptide, in the host cell.

Expression vector: A cloning vector that has been constructed in such a way that, after insertion of a DNA molecule, its coding sequence is properly transcribed and the RNA is translated. The cloned gene is put under the control of a promoter sequence for the initiation of transcription and often also has a transcription termination sequence at its end.

Feed: food for animals.

Food additive: any substance not normally consumed as food by itself and not normally used as a typical ingredient of food, whether or not it has nutritive value. The intentional addition to a food is for a technological purpose in the manufacture, processing, preparation, treatment, packaging, transport or holding of such food results, or may be expected to result (directly or indirectly) in it or its byproducts becoming a component of or otherwise affecting the characteristics of such foods.

Food: any substance, whether processed, semi-processed, or raw that is intended for human consumption and any substance that has been used in the manufacture, preparation or treatment of "food" which would also be consumed.

Food processing enzyme: Enzyme used to control food texture, flavor, appearance, or nutritional value.

Functional foods: any foods or food ingredient that may provide a health benefit beyond the traditional nutrients it contains.

Gene: The unit of heredity transmitted from generation to generation during sexual or asexual reproduction. More generally, the term is used in relation to the transmission and inheritance of particular identifiable traits. The simplest gene consists a segment of nucleic acid that encodes an individual protein or RNA.

Gene addition: The addition of a functional copy of a gene to the genome of an organism.

Gene amplification: The selective production of multiple copies of one gene

Gene Expression: The process through which a gene is activated at a particular time and place so that its functional product is produced.

Gene flow: The spread of genes from one breeding population to another related population by migration, thereby generating changes in allele frequency.

Gene Transfer: The transfer of genes to an organism. Usually used in terms of transfer of a gene to an organism other that the original organism, through the tools of biotechnology.

Genetic Code: A term used to describe the linear sequence of nucleotides (G, C, A and T) that make up DNA.

Genetic Engineering: The deliberate modification of the characteristics of an organism by manipulating its genetic material (DNA/RNA). The techniques used to transfer genes from one organism to another or to change genetic material within an organism.

Genetic marker: A DNA sequence used to identify a particular location (locus) on a particular chromosome. *See*: marker gene

Genetically Modified Foods: Any food containing parts of genetically modified plants, animals or microorganisms. There is some debate whether foods containing products from genetically modified organisms, but not parts of the organism themselves, should be classified as genetically modified foods. (For example, rennet, an enzyme used in cheese, can be produced from genetically modified microorganisms, but it does not actually contain any of the modified DNA.

Genetically Modified Organism: Any plant, animal, microorganism or virus which has been modified using genetic engineering techniques.

Genotype: the total genetic constitution of an organism. The allelic constitution at a particular locus, e.g. *Aa* or *aa*. The sum effect of all loci that contribute to the expression of a trait.

Good laboratory practice: Written codes of practice designed to reduce to a minimum the chance of procedural or instrument problems which could adversely affect a research project or other laboratory work.

Good manufacturing practice: Codes of practice designed to reduce to a minimum the chance of procedural or instrument/manufacturing plant problems which could adversely affect a manufactured product.

Hazard: A biological, chemical, or physical agent, or condition with the potential to cause an adverse health or environmental effect.

Hazard Characterization: The qualitative and /or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents.

Hormone: A specific chemical, produced in one part of a plant or animal body, and transported to another part where, at low concentrations, it promotes, inhibits or quantitatively modifies a biological process.

Host: An organism that contains another organism or a cloning vector. (Synonym: recipient organism)

Immune response: The processes, including the synthesis of antibodies that are used by vertebrates to respond to the presence of a foreign antigen. *See*: primary immune response; secondary immune response.

Immunity: The lack of susceptibility of an animal or plant to infection by a particular pathogen, or to the harmful effects of their toxins.

Immunization: The production of immunity in an individual by artificial means. Active immunization involves the introduction, either orally or by infection, of specially treated bacteria, viruses or their toxins so as to stimulate the production of antibodies.

Immunoassay: A detection system for a particular molecule, which exploits the specific binding of an antibody raised against it. For measurement, the antibody can incorporate a radioactive or fluorescent label, or be linked to an enzyme which catalyses an easily monitored reaction such as a change in color (*see*: ELISA).

Immunoglobulin E: A component of the human immune system implicated in the expression of allergies.

Inserted DNA: The segment of DNA that is introduced into chromosome, plasmid or other vector using recombinant DNA techniques.

Knockout: A mutant individual, in which a single functional gene has been replaced by a non-functional form of the gene. Used to understand gene function via the comparison of the phenotypes of wild type and knockouts.

Lipase: A class of enzymes which break down lipids into their component fatty acids and glycerol. Lipases used in biotechnology are generally digestive, with a role in the break-down of fats in food into their components, so that these can be used to make other materials.

Lipid: Any of a group of fats or fat-like compounds insoluble in water and soluble in fat solvents.

Liquid Chromatography: Analytical technique in which substances are separated based on their differential movement within a liquid stream.

Locus: The specific site on a chromosome at which a particular gene or other DNA landmark is located.

Macronutrients: In human and animals, a substance that is required in relatively large amounts for healthy growth and development, and belongs to one of 3 groups: carbohydrates, fats and proteins.

Marker: An identifiable DNA sequence that is inherited in Mendelian fashion, and which facilitates the study of inheritance of a trait or a linked gene.

Marker gene: A gene of known function or known location, used for marker-assisted selection or genetic studies.

Metabolism: The biochemical processes whereby nutritive material is converted to living matter, or aids in building living matter, or by which complex substances and food are broken down into simple substances.

Metabolite: A low-molecular-weight biological compound that is usually synthesized enzymically.

Micro array: A microscopic, ordered array of nucleic acids, proteins, small molecules, cells or other substances that enables parallel analysis of complex biochemical samples.

Micronutrient: In humans and animals a substance such as a vitamin or trace element, essential for healthy growth and development but required only in minute amounts.

Modification: Enzymatic attachment of one or more chemical groups to a macromolecule, affecting its biological activity or properties.

Modern biotechnology The application of: a. In vitro nucleic acid techniques, including recombinant deoxyribonucleic acid techniques and direct injection of nucleic acid into cells or organelles, or b. Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in

traditional breeding and selection. In contrast to traditional biotechnologies such as fermentation, plant breeding, irradiation, mutagenesis.

Molecular biology: The study of living processes at the molecular level.

Molecule: The stable union of two or more atoms; some organic molecules contain very large numbers of atoms.

Non-target organism: An organism which is affected by a treatment (e.g. pesticide application) for which it was not the intended recipient.

Novel substances: a new substance can be a known component such as protein, fat, carbohydrate, or vitamin which is novel in the context of that recombinant-DNA plant as well as a new metabolite resulting from the activity of enzymes generated by the expression of the introduced DNA.

Nucleotide: Nucleotides are the fundamental subunits from which DNA and RNA molecules are assembled. A nucleotide is a base molecule (adenine, cytosine, guanine and thymine in the case of DNA) linked to a sugar molecule and ribose or deoxyribose phosphate group for RNA or DNA respectively.

Nutrient density: Nutrient dense foods are those that provide substantial amounts of vitamins and minerals and relatively fewer calories. The opposite of nutrient dense is calorie dense which is foods that mainly supply calories and relatively few nutrients.

Nutrient deficiency: Absence or insufficiency of an essential factor for normal growth and development.

Nutritionally Improved or Quality Trait Crops: Food or feed crops in which the quantity, ratio and /or bioavailability is enhanced for either essential macro- and /or micronutrients or other compounds that indicates that they play a significant role in maintenance of optimal health, growth and development.

Pesticide: A toxic chemical product that kills pests (e.g. insecticides, fungicide, herbicides, rodenticides).

Phenotype: The observable characteristics of an organism. The visible and/or measurable characteristics of an organism (how it appears outwardly) as opposed to its genotype, or genetic characteristics.

Plasmid: A circular self-replicating non-chromosomal DNA molecule found in many bacteria, capable of transfer between bacterial cells of the same species, and occasionally of different species. Antibiotic resistance genes are frequently located on plasmids. Plasmids are particularly important as vectors for genetic engineering.

Polysaccharide: a linear or branched polymer (starch, cellulose, etc) composed of covalently linked monosaccharide, including cellulose, pectin and starch.

Prokaryote: a member of a large group of organisms, including bacteria and blue-green algae, in which the chromosome is not enclosed within a nucleus, but instead exists as a linear or circular strand.

Promoter: A DNA sequence that is located in front of a gene that controls mRNA transcription.

Protein: Biological effect or molecules that consist of one or more polypeptide chains of amino acid subunits encoded by an organism's genome. A macromolecule composed of one or more polypeptides, each comprising a chain of amino acids linked by peptide bonds.

Protease: An enzyme that catalyses the hydrolysis of proteins, cleaving the peptide bonds that link amino acids in protein molecules. *Synonym*: peptidase.

Protoplast: A bacterial or plant cell for which the cell wall has been removed either chemically or enzymatically, leaving its cytoplasm enveloped by a peripheral membrane. Protoplasts are spherical and smaller than the elongate, angular shaped and often vacuolated cells from which they have been released.

Ration: A fixed allowance of food or feed.

Recombinant: A term used in both classical and molecular genetics. 1. In classical genetics: An organism or cell that is the result of meiotic recombination. 2. In molecular genetics: A hybrid molecule made up of DNA obtained from different organisms. Typically used as an adjective, e.g. recombinant DNA.

Recombinant DNA: A DNA molecule formed by joining DNA segments from different sources.

Recombinant-DNA Plant: means a plant in which the genetic material has been changed through in vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles.

Restriction Enzyme: An enzyme derived from bacteria that cleave DNA at a unique specific sequence of nucleotides.

Risk: A function of the probability of an adverse health effect and the severity of that effect, which is consequential to a hazard(s).

Risk Analysis: A process consisting of 3 components: risk assessment, risk management and risk communication.

Risk Assessment: A scientific based process including the following steps: hazard identification, hazard characterization, exposure assessment and risk characterization.

Risk Characterization: The qualitative and /or quantitative estimation including attendant uncertainties of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment.

Risk Communication: The interactive exchange of information and opinions throughout the risk analysis process concerning hazards and risks, risk-related factors and risk perceptions, among risk assessors, managers, population, industry and academic community and other parties, including the explanation of risk assessment findings and the basis of risk management decisions.

Risk Management: The process of weighing policy alternatives considering risk assessment and other factors relevant for the health protection of population and for the promotion of fair practices, and if needed selecting appropriate prevention and control options.

Ribonucleic Acid: A nucleic acid molecule comprising a linear chain made up from 4 nucleotide subunits. Similar to DNA but differ in the makeup of nucleotides.

Ruminant: Animal having a rumen - a large digestive sac in which fibrous plant material is fermented by commensal microbes, prior to its digestion in a "true" stomach (the *abomasum*). Common farm ruminants are cattle and sheep.

Secretion: The transport of a molecule from the inside of a cell through the cell membrane.

Seed storage proteins: Proteins accumulated in large amounts in protein bodies within seeds. They act as a source of amino acids during germination. Of interest in biotechnology: 1. As a major source of human and animal nutritional protein. 2. As a model expression system. Since they are produced in large amounts relative to other proteins, and are stored in stable, compact bodies in the plant seed, it may be possible to engineer transgenes which are expressed in the same way as seed storage proteins - i.e. in large amounts and in a convenient form.

Segregant: An individual derived from a cross between two unlike parents.

Segregation: For genes, the separation of allele pairs from one another and their resulting assortment into different cells at meiosis. For chromosomes, the separation and re-assortment of the two homologues in anaphase of the first meiotic division. For individuals, the occurrence of different genotypes and/or phenotypes among offspring, resulting from chromosome or allele separation in their heterozygous parents.

Sequence: The linear order of nucleotides along a DNA or RNA molecule, and the process of obtaining this. Genome sequencing aims to generate the linear order of all nucleotides present in the nuclear DNA of an organism.

Serology: The study of serum reactions between an antigen and its antibody. Mainly used to identify and distinguish between antigens, such as those specific to particular micro-organisms or viruses.

Serum: Blood plasma that has had its clotting factor removed.

Somaclonal variation: Epigenetic or genetic changes induced during the callus phase of plant cells cultured *in vitro*, sometimes visible as changed phenotype in plants regenerated from culture.

Southern blot: A nitrocellulose or nylon membrane to which DNA fragments previously separated by gel electrophoresis have been transferred by capillary action.

Southern hybridization: A procedure in which a cloned, labeled segment of DNA is hybridized to DNA restriction fragments on a Southern blot.

Substantial equivalence: A concept widely used to measure whether a new food, product, or crop shares similar health and nutritional characteristics with its conventional counterpart.

Sub-chronic toxicity: Adverse effects resulting from repeated dosage or exposure to a substance over a short period, usually about 10 % of the life span. The capacity to produce adverse effects following sub-chronic exposure.

Tissue: A group of cells of similar structure which sometimes performs a special function.

Tissue culture: The *in vitro* culture of cells, tissues or organs in a nutrient medium under sterile conditions.

Toxicity: 1. Capacity to cause injury to a living organism defined with reference to the quantity of substance administered or absorbed, the way in which the substance is administered (inhalation, ingestion, topical application, injection) and distributed in time (single or repeated doses), the type and severity of injury, the time needed to produce the injury, the nature of the organism(s) affected and other relevant conditions. 2. Adverse effects of a substance on a living organism defined with reference to the quantity of substance administered or absorbed, the way in which the substance is administered (inhalation, ingestion, topical application, injection) and distributed in time (single or repeated doses), the type and severity of injury, the time needed to produce the injury, the nature of the organism(s) affected, and other relevant conditions.
RT acute toxicity, chronic toxicity, sub acute toxicity, sub chronic toxicity.

Toxin: A compound produced by one organism, which is deleterious to the growth and/or survival of another organism of the same or different species.

Trait: One of the many characteristics that define an organism. The phenotype is a description of one or more traits. *Synonym:* character.

Transgene: A gene used to transform an organism. Often, but not always, the transgene has been derived from a different species than that of the recipient.

Transgenesis: The introduction of a gene or genes into cells, which leads to the transmission of the input gene **(**transgene) to successive generations.

Transgenic: An individual in which a transgene has been integrated into its genome. In transgenic eukaryotes, the transgene must be transmitted through meiosis to allow its inheritance to its offspring.

Transformation: The uptake and integration of DNA in a cell, in which the introduced DNA is intended to, change the phenotype of the recipient organism in a predictable manner. Transformation can occur naturally in nature or artificially in a laboratory.

Vaccine: A preparation of dead or attenuated (weakened) pathogens, or of derived antigenic determinants, that can induce the formation of antibodies in a host, and thereby produce host immunity against the pathogen. *See*: sub-unit vaccine, viral vaccine, DNA vaccine, inoculums

Variety: 1. a subdivision of a species, with distinct morphological characters. 2. A defined strain of a crop plant, selected on the basis of phenotypic (sometimes genotypic) homogeneity.

Vector: 1. an organism, usually an insect that carries and transmits pathogens. 2. A small DNA molecule (plasmid, virus, bacteriophage, artificial or cut DNA molecule) that can be used to deliver DNA into a cell. Vectors must be capable of being replicated and contain cloning sites for the introduction of foreign DNA.

Vitamin: Naturally occurring organic substance required by living organisms in small amounts to maintain normal health.

Viral Vaccine: vaccine consisting on living viruses, genetically engineered to avoid causing the disease itself.