ANIMAL PROTEIN CROP
STEWARDSHIP

Guide for Maintaining Plant Product integrity of Biotechnology-Derived Animal Protein Crops

APCS is a program for Stewardship of Plant Molecular Farming Products Expressing Animal Proteins in Crops used for Food and Feed

DISCLAIMER

The *Guide for Maintaining Plant Product Integrity of Biotechnology-Derived Animal Protein Crops* ("Guide") is solely an educational tool and is guidance to assist users in developing and implementing their own organization-specific stewardship program for these products.

The Guide is flexible, and its application will differ according to the size, nature and complexity of the organization and products involved. The Guide is representative and not exhaustive. It is the responsibility of any user of this Guide to consider that user's specific circumstances (1) when developing a stewardship program specific to its organization, and (2) in meeting any applicable legal requirements.

This Guide is not, and should not be used as, a substitute for (1) a user's own individual understanding of its legal requirements, (2) consultation by a user with its legal counsel and other advisors, or (3) direct contact with appropriate regulatory agencies.

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Introduction

The APCS Guide for Maintaining Plant Product Integrity of Biotechnology-Derived Plant Products provides information on how to develop and implement a stewardship program and quality management system that will assist organizations in maintaining plant product integrity of biotechnology-derived plant[1] products at various stages from research and discovery through commercialization and post-market activities.

The maintenance of product integrity is critical for achieving compliance with regulatory requirements, fulfilling customer expectations, and preventing trade disruptions. Even small amounts of material out of place can have serious consequences for a product developer and commercial trade. Examples of material out of place include adventitious presence (AP) and low-level presence (LLP). Managing AP and LLP throughout the product life cycle is an important component of maintaining plant product integrity. Regulations vary by country or region and organizations using this guide are encouraged to check with their local authority for all applicable regulations.

Purpose

The Guide has been developed as a series of informative educational modules that mirror the product life cycle and can be adapted to develop and improve an organization's stewardship program and quality management system (QMS) for biotechnology-derived products. Common to all the modules is an emphasis on the importance of product identification and traceability as well as documentation and data governance.

[1] This document defines plant as any plant (including plant part) for or capable of propagation. Various references are made to seed and seed production methods and crop management. It is recognized that systems exist where plant production may be accomplished through non-seed-based methods such as vegetative propagation, and therefore the use of the term "seed" is not meant to limit the scope of this document.

Scope

This Guide addresses stewardship and quality management systems for the full life cycle of biotechnology-derived plant products. It is applicable to all stages of the plant product life cycle from initial research and discovery, through development and registration, and during commercialization and post-market activities.

The guidance in this document is intended to be flexible and its application will differ according to the size, nature, and complexity of the organization involved. Some of the information contained within this document specifically addresses products of biotechnology that are derived through plant transformation.

Format of this Guide

This Guide begins with a section dedicated to stewardship principles that are applicable across all stages. After this, and to accommodate different business models, the Guide is sectioned into the seven stages of the product life cycle for biotechnology-derived plant products:

Stage 1	Research and Discovery
Stage 2	Product Development
Stage 3	Seed or Plant Production
Stage 4	Marketing and Distribution
Stage 5	Crop Production
Stage 6	Crop Utilization
Stage 7	Product Discontinuation

Stewardship Principles Across Modules

This section provides guidance for the development and implementation of a process-based stewardship program and quality management system (QMS) to support research, development, and commercial activities for biotechnology-derived plant products. Quality Management consists of the systems, processes, and documented information needed to establish stewardship and maintain quality in each phase of the product life cycle. The QMS should be tailored to the type and scope of operations for an organization, and development of a QMS should begin in early stages of project planning, and continue throughout development, breeding, production, and commercial activities.

Note that the critical control points outlined in each of the modules should be assessed during development of the QMS. The selection and extent of the preventive measures for each of the identified critical control points should be determined by considering the nature of the process or product and associated aggregate controls. The extent, nature of, and points of application of the control measures should be determined and customized by each organization.

Developing and implementing a documented QMS for biotechnology-derived plant products consists of multiple steps as described below. The following steps have been incorporated as the foundation for this Guide:

- Quality policy and objectives: Establish and communicate the quality policy and quality objectives (including integrity of the biotechnology-derived plant products) of the organization, possibly based on a risk and opportunities assessment and on regular alignment within management teams.
- Customer expectations: Determine the needs and expectations of customers and other stakeholders in the overall context of the organization. Stakeholders may include regulators, licensees, business partners, growers, and other members of the value chain whose business interests may be affected by the development and commercialization of biotechnology-derived plant products.
- Quality objectives: Determine the processes and responsibilities necessary to reach the quality objectives.
- Resources: Determine and provide the resources necessary to reach the quality objectives.

- Critical Control Points (CCPs) and relevant actions for verification of Plant Product Integrity (PPI): Establish the CCPs and necessary procedures, actions, and relevant records for each Critical Control Point (CCP).
- Training: Determine a training process and provide the trainings necessary to relevant personnel to ensure they have the required competencies and skills to perform activities in the defined processes. Develop and implement measures to assess the efficiency of the trainings.
- Documentation: Determine, develop, and update the relevant documented information needed to ensure the effective implementation of each process. Implement a specific process to ensure the management and control of such documented information. The aim is to have documented information that is relevant and readable; controlled to maintain content integrity; clearly and consistently identified; deployed to relevant users; reviewed in a timely manner and retrievable.
- Metrics and periodic auditing/assessments: Determine and implement measures, key performance indicators, and audit processes to assess the effectiveness, efficiency, and conformance of each process.
- Management of nonconformities: Determine and implement means for preventing nonconformities and noncompliance and eliminating their causes.
- Continuous improvement: Develop, establish, and implement a process for continuous improvement of the quality management system including annual management reviews, processes reviews (with a re-assessment of risk and opportunities).

Resources to Address Principles

ISO 9001-2015[2]

The International Organization for Standardization (ISO)[3] family of standards collectively provides a framework that an organization may use to develop, implement, and maintain quality management systems.

ISO identifies seven management principles that can be used to lead an organization towards improved performance. These principles are the basis of the standards for quality management systems within the ISO 9000 family:

QMS Principles	Customer Focus
	Leadership
	Staff Involvement
	Process Approach
	Improvement
	Evidence-based Decision Making
	Stakeholders Relation Management

The requirements for quality management systems as specified in ISO 9001:2015 are universal and can be applied by any organization that wishes to establish a quality management system for biotechnology-derived plant products.

[2] This does not imply that this Guide is compliant with ISO standards. Furthermore, an organization is not required to be ISO-certified to successfully complete an ETS Audit but must have a functional QMS in place.
[3] http://www.iso.org/iso/home/about.htm

HACCP[4]

The Hazard Analysis and Critical Control Point (HACCP)[5] system is an internationally accepted, science-based, and systematic tool to assess risks and hazards and to establish control systems that focus on prevention rather than on end-product testing.

The HACCP system consists of the seven principles listed below, applied in a logical sequence:

Principle 1	Conduct a hazard analysis.
Principle 2	Determine the Critical Control Points.
Principle 3	Establish critical limit(s).
Principle 4	Establish a system to monitor control of the CCP.
Principle 5	Establish the corrective action to be taken when monitoring indicates that a particular CCP is not under control.
Principle 6	Establish procedures to verify that the HACCP system is working effectively.
Principle 7	Establish documentation concerning all procedures and records appropriate to these principles and their application.

GLP[6]

Good Laboratory Practices (GLP) establish a set of standards, practices, records required for lab, containment facilities, and field activities. GLP can be supportive of QMS and ISO and may be required for regulatory submissions.

[4] As with ISO, it is not required to be HACCP-certified to successfully complete an ETS Audit.
[5] CAC. 1997. Hazard Analysis and Critical Control Point (HACCP) System and Guidelines for its Application: Annex to CAC/RCP 1-1969, Rev.3 (1997). Codex Alimentarius Commission (CACV), Geneva. http://www.fao.org/docrep/004/y1579e/y1579e03.htm
[6] As with HACCP, it is not required to be GLP-certified to successfully complete an ETS Audit.

Inventory Systems

Integral to quality management systems that address plant product integrity is the implementation of an inventory system. Inventory systems should effectively manage traceability of all materials identification, labeling[7], tracking, and disposition[8] (e.g., of plasmids, constructs, plantlets, samples, plants, and seed). This is essential to retrieve information pertinent to the identity, location, and quantity of these materials at any given time throughout the product life cycle for biotechnology-derived materials.

For example, in the laboratory, organizations may employ a commercial or customized Laboratory Information Management System (LIMS) designed specifically for research and development labs. Typically, a LIMS connects analytical instruments in the lab to one or more workstations or personal computers where data is collated, sorted, and organized into various report formats based on the type of report required. Smaller organizations could select a manual or automated inventory management system that includes procedures for sample identification. This can include features such as the generation of sample labels; generation of replacement labels; tracking changes in status (for example, sample in storage, sample discontinued); linking sub-samples to source samples; and tracking container-to-container transfers (e.g., for plant tissue culture).

Identity Confirmation

For the purposes of this Guide and unless otherwise indicated, identity confirmation may be achieved using either or both of the following:

- Procedural confirmation (e.g., documentation, phenotypic evaluations)
- Analytical confirmation (e.g., laboratory assays)

This will be determined based on individual circumstances and may warrant a case-by-case assessment. It is noted that while phenotypic evaluations can be conducted (e.g., phenological verification involving application of herbicides to verify herbicide tolerance), prudence should be exercised with these methods since results will not be specific to one event (not event specific). Moreover, as technology develops, additional acceptable confirmation measures may be established.

[7] For the purposes of this guide, labeling means to affix with a label that is marked with a name and/or other identifying information (e.g., bar code) that can be used to confirm construct or transformant identity.
[8] Describes what was done with the plant material (e.g., planted, destroyed, devitalized, buried, stored, sold, cultured, processed for analysis or manufacture).

Examples of Forms

Global Stewardship Group program participants have access to examples of forms that can be customized for documentation of their various processes. For more information, contact info@gsg.ag.

Guidance for Using Stages

An organization may be involved in one or more activities associated with the development and commercialization of a biotechnology-derived plant. For example, a platform company may limit its business to construct development, whereas another organization may have multiple integrated functions bridging from the laboratory to commercial production and sales. The organization can adopt the sections of this guide that are applicable to its own individual circumstance. Each stage covers activities with shared operational and regulatory considerations.

Stage 1: Research and Discovery - Applicable for all Developers

The *Research and Discovery* stage includes activities that identify and evaluate the specific genes, proteins, and other elements that may be used to produce or construct a new plant product through biotechnology. Stewardship for this stage of the product life cycle includes ensuring that the processes for design and construction result in the intended material and that integrity is maintained.

Construct Development

a) Develop, Establish and Implement Preventive Measures for:
    i. Processes for the design of the construct prior to production.
    ii. Verification of the identity and integrity of the construct (e.g., using sequencing, restriction endonuclease mapping, polymerase chain reaction using construct-specific oligonucleotides, Southern blot with construct-specific probes or other appropriate methods).
    iii. Labeling, tracking, and disposition as part of an inventory system for constructs.
    iv. Procedures so that labels used to identify a construct are recorded and information pertinent to the construct's identity is retrievable.
    v. Internal work processes and documented information for traceability.
b) Develop, Establish and Implement Monitoring and Verification Procedures to:
    i. Verify the integrity of the construct as designed.
    ii. Confirm identity prior to transfer for plant transformation.
c) Develop, Establish and Implement Corrective Measures for:
    i. When a construct is found to be incorrectly identified or where the identity cannot be confirmed as originally designed. Review and determine the disposition of the construct and derivations.
    ii. Incorporating any corrective measures or procedural changes into work processes and documented information.
    iii. Training personnel on the procedural changes incorporated.
d) Develop, Establish and Implement Record Keeping and Documentation Procedures:
    i. Documentation of identity and traceability should be secure, accessible, and retained.
    ii. Inventory systems should effectively manage traceability of all materials identification, labeling, tracking, and disposition (e.g., of plasmids, constructs, and samples).

Plant Transformation and Regeneration

a) Develop, Establish and Implement Preventive Measures for:
    i. Labeling, tracking, and disposition as part of an inventory system for transformants (events).
    ii. Procedures so that labels used to identify host material and transformants are recorded and information pertinent to identity is retrievable.
    iii. Internal work processes and documented information for traceability.
b) Develop, Establish and Implement Monitoring and Verification Procedures:
    i. Prior to transformation, confirm identity of transforming DNA, host, and associated material by documentation or confirm using diagnostic methods.
    ii. During steps to regenerate plant, confirm identity of transformant by documentation or confirm by diagnostic methods.
    iii. Prior to transfer for further propagation, confirm identity of transformant by documentation or confirm by diagnostic methods.
    iv. Processes and criteria for the selection of transformants.
c) Develop, Establish and Implement Corrective Measures for:
    i. When the host material or the transformant is found to be incorrectly identified or the identity cannot be confirmed. Review the material and any derivatives, and determine appropriate disposition.
    ii. Incorporating any corrective measures or procedural changes into documented information.
    iii. Training personnel on procedural changes incorporated.
d) Develop, Establish and Implement Incident Escalation and Response Procedures:
    i. Procedures in place to report and escalate any incidents of loss of control or containment of GM traits.
    ii. Documentation to ensure that personnel are trained on procedures.
e) Develop, Establish and Implement Record Keeping and Documentation Procedure:
    i. Records of transformation, regeneration, identity, and traceability should be secure, accessible, and retained as appropriate.
    ii. Inventory systems should effectively manage traceability of all materials identification, labeling, tracking, and disposition (e.g., of plasmids, constructs, plantlets, plants, samples, and seed).
    iii. Procedures for the retention of documentation related to nonconformities and follow up actions.

Stage 2: Product Development - Applicable for all Developers

The *Product Development* stage includes activities that occur before a biotechnology-derived plant product is commercialized. These activities include, but are not limited to, the continuation of plant transformation and regeneration, event selection in contained facilities or confined field trials, and event evaluation to determine suitability for intended use and to generate data for regulatory submissions. At this stage, ensure availability of relevant diagnostic tests to confirm product identity and to address determined needs. Stewardship for this stage of the life cycle includes ensuring that systems are in place to maintain plant product integrity, achieve regulatory compliance, manage product launch, and plan for effective and proper product use to sustain its value.

Containment Facilities

a) Develop, Establish and Implement Preventive Measures for:
    i. Space assignment within the facility.
    ii. Labeling, tracking, and disposition of propagatable plant material as part of an inventory system.
    iii. Procedures so that labels used to identify plants are recorded and information pertinent to identity is retrievable.
    iv. Internal work processes and documented information for traceability.
    v. Methods and controls for reproductive isolation within the facility (where applicable), for containment, and for effective devitalization and disposal (e.g., equipment and facility design and maintenance; equipment and facility cleaning).
b) Develop, Establish and Implement Monitoring and Verification to:
    i. Review space assignment criteria.
    ii. Confirm plant identity prior to transfer to, within, or from containment facilities by documentation or verify using diagnostic methods where appropriate.
    iii. Monitor facility at regular intervals so that the appropriate level of containment is maintained and features that are designed to ensure containment are not compromised.
c) Develop, Establish and Implement Corrective Measures:
    i. When plants are found to be incorrectly identified, where identity cannot be confirmed, or where reproductive isolation has not been maintained. Review the plant material and any parental, progeny, samples, and/or associated materials and determine the appropriate disposition.

ii. Correct any deficiencies identified that could affect the integrity of the materials or containment facility.
iii. Correct any deficiencies identified that could affect reproductive isolation or appropriate separation of plant material.
iv. Incorporate any corrective measures or procedural changes into documented information.
v. If applicable, train personnel on the procedural changes incorporated.

d) Develop, Establish and Implement Incident Escalation and Response Procedures:
   i. Procedures in place to report and escalate any incidents of loss of control or containment of GM traits.
   ii. Documentation to ensure that personnel are trained on procedures.
e) Develop, Establish and Implement Record Keeping and Documentation Procedures:
   i. Documentation of analyses, identity, and traceability should be secure, accessible, and retained, as appropriate.
   ii. Procedures for the retention of records related to nonconformities and follow up actions.
   iii. Inventory systems should effectively manage traceability of all materials identification, labeling, tracking, and disposition (e.g., of plantlets, plants, samples, and seed).

Confined Field Trials

a) Develop, Establish and Implement Preventive Measures for:
   i. Site selection and planning for the controlled environmental release.
   ii. Labeling, tracking, and disposition of plant material as part of an inventory system.
   iii. Procedures to ensure that labels used to identify plants or seeds are recorded and information pertinent to identity is retrievable.
   iv. Internal work processes and documented information for traceability.
   v. Transfer protocols or processes for traceability across functions, departments, organizations, or locations.
   vi. Protocols and/or documented information for planting (e.g., procedures to ensure any equipment used for planting is free from contaminant seed/material prior to and following use; the plot design is clear and easy to follow to prevent errors such as the wrong genotype planted in the wrong location of plot).
   vii. Protocols and/or documented information for harvesting of the plant material to prevent cross contamination from other genotypes from both

within the plot, or from other sources outside the plot (e.g., procedures to ensure any equipment or container (e.g., bag, bin, and envelope) used for harvest is free from contaminant seed/material prior to use).

viii. Methods and controls for confinement (e.g., those for reproductive isolation around the field trial site and within the field trial site if required for transgenic purity, those for movement of personnel and equipment between trials of different events during pollen flow, those for cleaning of equipment prior to it leaving the trial site, those for disposition of plant material during season or after harvest, and those for post-harvest land-use restrictions).

ix. Restrictions following completion of confined field trial activities (e.g., subsequent crop allowances, rotation restrictions).

x. Sufficient training, communication, and monitoring of activities related to confined field trials to ensure that plans are being followed and intentions involving confinement are being met.

b) Develop, Establish and Implement Monitoring and Verification Procedures to:
   i. Confirm:
      i. Plant identity prior to transfer to the field trial site.
      ii. Plant identity and assessment of transgenic purity of plant material from the trial site by documentation or by using diagnostic methods where appropriate.
      iii. Confinement measures through assessment.
   ii. Monitor the field-trial site at regular intervals to confirm that management practices to confine the field-trial site are implemented in accordance with regulatory and internal operational requirements.
   iii. Volunteer monitoring.
c) Develop, Establish and Implement Corrective Measures for:
   i. When a plant is misidentified, a plant is correctly identified but is not the desired genotype, or when identity cannot be confirmed. The plant material and any parental, progeny, samples, and/or associated materials should be reviewed, and appropriate disposition determined.
   ii. Correcting any deficiencies that could affect confinement of the field trial site and assess impact on plant product integrity.
   iii. Incorporating any corrective measures or procedural changes into the SOP, as appropriate.
   iv. Training, as applicable, personnel on the procedural changes incorporated.
   v. Incorporating reporting and resolution procedures for potential regulatory compliance incidents.
d) Develop, Establish and Implement Incident Escalation and Response Procedures:

i. Procedures in place to report and escalate any incidents of loss of control or confinement of GM traits.
ii. Documentation to ensure that personnel are trained on procedures.
iii. Ensure corrective actions are taken and documented. If applicable, report incident to appropriate regulatory authorities.

e) Develop, Establish and Implement Record Keeping and Documentation Procedures for:
   i. Documentation of trial conduct, identity and traceability should be secure, accessible, and retained as appropriate.
   ii. Methods should be established and implemented to develop and record the trial protocol to provide trial execution guidance, from planning through final disposition of harvested material.
   iii. Procedures for the retention of documentation related to nonconformities and follow up actions.
   iv. Processes to communicate changes in regulatory status and trial requirements to relevant parties. For example, the transition of confined field trials from regulated to stewarded status.
   v. Inventory systems should effectively manage traceability of all materials identification, labeling, tracking, and disposition (e.g., plants, samples, and seed).

Stage 3: Seed or Plant Production - Applicable for all Developers

The *Seed or Plant Production* stages include activities designed to ensure that plant products are grown according to defined standards to meet regulatory requirements and product specifications for integrity (i.e., identity, purity, and performance). Products at this stage could be unauthorized[9], stewarded[10], or fully authorized.

a) Develop, Establish and Implement Preventive Measures for:
   i. Effective processes and procedures supported by robust training.
   ii. Quality assurance and control processes to ensure seeds are properly tested and that results are recorded.
   iii. Labeling, tracking, and disposition of plant material as part of an inventory system.

[9] *Unauthorized*: Biotechnology-derived plant material or event that has not been authorized by the relevant competent authorities for release into the environment for purpose of cultivation or for use in the food and feed chains.
[10] *Stewarded:* In a country of cultivation, material that has received authorization for purpose of cultivation or for use in the food and feed chains, but is pending authorization from key import countries with functioning regulatory systems.

iv. Procedures so that labels used to identify seeds or plants are recorded and information pertinent to identity is retrievable.
v. Internal work processes and documented information for traceability.
vi. Transfer protocols or processes for traceability across functions, departments, organizations, or locations.
vii. **For all developers:** Methods and controls based on the growing region's proximity to direct export access (waterways, rail) and facilities that process like products for food.
viii. Methods and controls for reproductive isolation, as necessary (e.g., compliance with national standards for production of breeder, foundation, registered, and certified seed). **For products expressing animal proteins that are a major food allergen:** Appropriate isolation and buffer zones – based on the biology of the crop – should be deployed to minimize the potential for commingling and outcrossing.
ix. Methods and controls for appropriate equipment cleaning and sanitation. **For products expressing animal proteins that are a major food allergen:** Field equipment (e.g. planters, harvest implements) that comes into contact with these materials should be dedicated for use during the duration of the developer's growing cycle, or until such equipment has been appropriately cleaned. A developer should provide adequate cleaning procedures for any equipment that directly comes into contact with the material.
x. Methods and controls for appropriate seed storage, shipment, and disposal. **For products expressing animal proteins that are a major food allergen:** Developers should provide clear protocols to direct contracted growers' activities before planting, during the growing season, after harvest, and in the following season. They should have contractual obligations that cover all applicable stewardship practices, including with respect to the delivery of all harvested material to a specified location and that addresses all unused viable plant parts, such as seed or tubers, to the developer.
xi. Training for individuals involved with activities related to plant and seed multiplication, including where these are managed within confined field trials, if applicable.
xii. **For products expressing animal proteins that are a major food allergen:** A developer should design an audit and monitoring plan for its activities and conduct the specified monitoring and auditing activities before planting, during the season, at harvest, and post-harvest.

b) Develop, Establish and Implement Monitoring and Verification Procedures to:
   i. Confirm:

i. Seed or plant identity prior to transfer of seed or plant material to the field.
ii. Seed or plant identity and assessment of transgenic purity of seed or plant material from the field by documentation or by diagnostic methods where appropriate (this applies to plant material that may be used for further multiplication or planting).

ii. To implement methods and controls for:
i. appropriate post-harvest monitoring requirements. **For products expressing animal proteins that are a major food allergen:** The developer should consider appropriate restrictions on subsequent rotation crops to help allow for effective volunteer management and for potential downstream use considerations.
ii. Seed or plant identity during storage or shipment.

iii. Monitor the seed multiplication program to confirm that management practices (including reproductive isolation) are in place to meet internal operational requirements and external (e.g., seed certification agencies) standards for relevant seed classes (e.g., breeder, foundation, registered, and certified seed.

c) Develop, Establish and Implement Corrective Measures for:
i. When a plant is misidentified, a plant is correctly identified but is not the desired genotype, or when identity cannot be confirmed. The plant material and any parental, progeny, samples, and/or associated materials should be reviewed, and appropriate disposition determined.
ii. Correcting any deficiencies identified that could affect the reproductive isolation of the field sites and assess impact on plant product integrity.
iii. Incorporating any corrective measures or procedural changes into documented information as appropriate and ensure relevant personnel are trained.

d) Develop, Establish and Implement Incident Escalation and Response Procedures:
i. Procedures in place to report and escalate any incidents of loss of control of GM traits.
ii. Documentation to ensure that personnel are trained on procedures.

e) Develop, Establish and Implement Record Keeping and Documentation Procedures:
i. Records of production, identity, and traceability should be secure, accessible, and retained as appropriate.
ii. Procedures for the retention of records related to nonconformities and follow up actions.

iii. Inventory systems should effectively manage traceability of all seed materials identification, labeling, tracking, and disposition.

Stage 4: Marketing, Distribution, and Product Launch - Applicable for all Developers

The *Marketing and Distribution* stage includes activities related to the product launch, sales, and distribution of products through both the internal supply chain and the external distribution chains to customers. Prior to the commercial sale of any biotechnology-derived seed or plant product, the product developer or its licensee should have secured all necessary regulatory authorizations in the country of launch as well as in key import markets.

Marketing and Distribution

a) Develop, Establish, and Implement Preventive Measures for:
   i. Defining appropriate seed quality standards to be achieved in order that plants/seeds are suitable for their intended use.
   ii. Implementing an appropriate quality control strategy to ascertain seed quality standards are being fulfilled.
   iii. Labeling, tracking, and disposition of plant material as part of an inventory system for activities up to and including the point of commercial distribution.
   iv. Procedures so that information used to identify plant products is recorded on labels and associated with documentation pertinent to identity and production history.
   v. Internal work processes and documented information for traceability.
   vi. Transfer protocols or processes for traceability across functions, departments, organizations, and locations.
   vii. Protocols and processes for equipment cleaning and inspection to avoid inadvertent physical mixture (dedicated equipment should be considered where appropriate).
   viii. Seed processing, warehousing, and distribution processes to maintain plant product integrity and avoid inadvertent physical mixture.
b) Develop, Establish and Implement Monitoring and Verification Procedures to:
   i. Confirm plant identity prior to cleaning, packaging, and transport by documentation or verify using diagnostic methods where appropriate.
   ii. Verify that the plant product meets the quality standard for intended use.

c) Develop, Establish and Implement Corrective Measures for:
    i. Processes for product containment, withdrawal, and recall.
    ii. When plant material is misidentified, correctly identified but not the desired genotype, or where identity cannot be confirmed, determine appropriate disposition of the plant material and any parental, progeny, samples, and/or associated materials.
    iii. Processes for receiving, controlling, and determining the disposition of returned materials.
    iv. Incorporating procedural changes into standard operating procedures and train relevant personnel to prevent recurrence of nonconformities.
d) Develop, Establish and Implement Incident Escalation and Response Procedures:
    i. Procedures in place to report and escalate any incidents of loss of control of GM traits.
    ii. Documentation to ensure that personnel are trained on procedures.
    iii. Incorporate appropriate incident response protocols to ensure timely and accurate reporting of corrective actions.
e) Develop, Establish and Implement Record Keeping and Documentation Procedures:
    i. Procedures so that documentation of production, processing, distribution, identity, and traceability is secure, accessible, and retained as appropriate.
    ii. Procedures for the retention of documentation related to nonconformities and follow up actions.
    iii. Inventory systems should effectively manage traceability of all seed materials identification, labeling, tracking, and disposition.

Product Launch

There are several activities that an organization should consider in honoring its commitment to product launch stewardship. Not all of the activities outlined below may be applicable or necessary for all organizations. Appropriate functions within an organization (e.g., stewardship, marketing, legal, licensing, production, regulatory, research, supply chain, and communications) should be consulted in the process of designing product launch stewardship activities to meet the specific needs of its products and markets.

a) Product Launch Policy: An organization should develop a product launch stewardship policy that is suited to its business model, the nature of its products, and its product market(s). Such a policy will help guide the commercialization of biotechnology-derived products by directing, prior to product launch, due attention to regulatory approval requirements, market assessments, and other provisions.

b) Product Lauch Team: Identify person(s) in the organization responsible for product launch stewardship.
c) Market and Trade Assessment: Conduct a market and trade assessment to identify key markets and key import activities prior to commercial launch of any new biotechnology-derived plant product (crop by event) in any country. For products with intended special uses, additional factors to consider in conducting a market and trade assessment may include:
    i. The types and nature of the special use;
    ii. Whether the special use product has multiple uses and whether unique handling, distribution or other operational conditions exist;
    iii. Characterization of the product process or ingredient flows;
    iv. Whether significant, unintended processing, product functional or compositional negative effects are likely to be caused; and
    v. Whether the product might be exported as grain, processed fractions or food/feed end products.
d) Develop regulatory and commercialization plans to meet applicable regulatory requirements in key production and importing countries (as determined by the market and trade assessment) prior to commercialization of a new biotechnology-derived product.
e) Communicate broadly and transparently with stakeholders and employees regarding plans for company-specific product launch stewardship and their implementation.

Stage 5: Crop Production - (a) is Applicable to all Developers; (b) applies only to Developers with Products Expressing Animal Proteins that are Major Food Allergens

The *Crop Production* stage includes activities involved in the cultivation for harvest of an authorized, commercially available biotechnology-derived commodity.

a) **Applies to All Developers -** Geography: Consider the growing region's proximity to direct export access (waterways, rail) and facilities that process like products for food, and implementation of risk-based controls.
b) **Applicable only to developers with products expressing animal proteins that are a major food allergen -** On-Farm Crop Production and Field Operations:

i. Appropriate isolation and buffer zones: Appropriate isolation and buffer zones – based on the biology of the crop – should be deployed to minimize the potential for commingling and outcrossing.
ii. Management of crop production: Developers should provide clear protocols to direct contracted growers' activities before planting, during the growing season, after harvest, and in the following season. They should have contractual obligations that cover all applicable stewardship practices, including with respect to the delivery of all harvested material to a specified location and that addresses all unused viable plant parts, such as seed or tubers, to the developer.
iii. Equipment: Field equipment (e.g. planters, harvest implements) that comes into contact with the materials should be dedicated for use during the duration of the developer's growing cycle, or until such equipment has been appropriately cleaned. A developer should provide adequate cleaning procedures for any equipment that directly comes into contact with the material.
iv. Post-harvest land use restrictions: A developer should consider appropriate restrictions on subsequent rotation crops to help allow for effective volunteer management and for potential downstream use considerations.
v. Specialized performance auditing and monitoring: A developer should design an audit and monitoring plan for its activities and conduct the specified monitoring and auditing activities before planting, during the season, at harvest, and post-harvest.

Stage 6: Crop Utilization - (a) is Applicable to all Developers; (b) applies only to Developers with Products Expressing Animal Proteins that are Major Food Allergens

The *Crop Utilization* stage includes the use of biotechnology-derived plant product commodities for food, feed, fiber, or other purposes (e.g., biofuels, industrial applications).

a) **Applicable to all developers:** Transportation and Storage of Viable Products - Develop Processes, Protocols or Procedures for*:*
    i. Equipment dedicated to the material for duration of use: Assess relevant procedures to limit the potential for unintended presence of these products through the use of equipment dedicated to these materials. This includes

equipment used to transport plant material, such as but not limited to trailers, hoppers and bins.

ii. Controls for managing post-harvest movement of plant material: Consider the relevant controls for managing post-harvest plant parts, such as but not limited to grain and tubers movement to enable traceability.

iii. Storage dedicated to the material for duration of use: Until cleaning has been verified, storage areas for the plant material should be dedicated only to that material.

iv. Rapid assay: A detection method for stored materials.

b) **Applicable only to developers with products expressing animal proteins that are a major food allergen:** Producing Material in Processing Facilities. Processes, Protocols or Procedures for:

i. Contractual agreements: Processing agreements that address segregation and identity preservation.

ii. Storage dedicated to the materials for duration of use: Until cleaning has been verified, storage for these materials should be dedicated to that use.

iii. Processing lines and equipment dedicated to the materials for the duration of use: Processing lines and equipment dedicated to use until cleaning has been verified.

iv. Detection method: A detection method to ensure equipment has been appropriately cleaned.

v. Sanitation program: Effective and verified sanitation.

vi. Waste collection and disposal: Appropriate waste collection and disposal.

Stage 7: Product Discontinuation - Applicable for all Developers

The *Product Discontinuation* stage includes activities involving authorized commercialized biotechnology-derived plant products that have reached the end of their commercial life cycle and all sales of materials under the organization's control have been terminated where applicable. Product discontinuation is recognized by the plant biotechnology industry as a routine part of the product life cycle and is different from product withdrawals and recalls. The discontinuation of a product is a business decision and considers many factors. These include prevailing regulatory requirements, market forces and product replacement.

a) Identify Discontinuation Management Team: Due to the complex nature of a product discontinuation, a multi-disciplinary team, committee, or group is responsible for developing and implementing the discontinuation plan.
b) Develop & Implement Discontinuation Plan: A discontinuation plan is a key document for the coordination of the discontinuation and includes key actions, deliverables, timelines, and responsibilities. Based on the scope, the discontinuation plan should address geography-specific and function-specific needs, enabling alignment throughout the discontinuation process.
c) Verify & Communicate Discontinuation Completion: The completion of the product discontinuation needs to be verified according to the verification strategy defined within the discontinuation plan.
    i. A review of the discontinuation plan and verification that important actions have been completed and documented (e.g., documentation of utilization and/or disposition of seed stock).
    ii. A verification that planned audits have been completed and findings have been addressed. A final audit of facilities, records and other relevant materials may be completed.

Guide Summary

The APCS Guide for Maintaining Plant Product Integrity provides information on how to develop and implement a stewardship program and quality management system that will assist organizations in maintaining plant product integrity of biotechnology-derived plant products at various stages from research and discovery through commercialization and post-market activities. The guidance in this guide was intended to be flexible and its application could differ according to the size, nature, and complexity of the organization involved. It is intended that program participants establish procedures based on the content of this Guide for each relevant stage of their product life cycle for these products.

Abbreviations/Acronyms

AP	Adventitious Presence
CACCP	Containment Analysis and Critical Control Point
CCP	Critical Control Point
CCPs	Critical Control Points
DNA	Deoxyribonucleic acid
GM	Genetically Modified
HACCP	Hazard Analysis and Critical Control Point
ISO	International Organization for Standardization
LIMS	Laboratory Information Management System
LLP	Low-level Presence
OECD	Organization for Economic Co-operation and Development
PPE	Personal Protective Equipment
PPI	Plant Product Integrity
QMS	Quality Management System
SOP	Standard Operating Procedure
USDA	United States Department of Agriculture

Definitions

Adventitious presence: Unintentional and incidental presence of trace amounts of one or more biotechnology-derived traits in seed, grain, or food product.

Authorization: An approval, clearance, or other grant of authority that comes from a responsible governmental entity and covers a particular article, product, or activity. This may include authorization to transport plant material between states, conduct confined field trials, and release biotechnology-derived plants for the purpose of cultivation.

Batch: Materials produced at a single stage of production.

Biotechnology(-derived): Per the Convention on Biological Diversity, biotechnology is the application of a) *in vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) 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. Other technologies not specifically included in the above definition may be subject to regulation and/or additional stewardship considerations. (See **Transgenic**)

Breeder seed: A class of seed or vegetative propagating material, increased by the originating, sponsoring plant breeder or institution, used as basic or the first source of seed for further seed increase.

Certified seed: a) Seed of a cultivar that has been verified for its genetic identity and purity by visual inspection by an official seed-certifying agency. Classes of certified seed are breeder, foundation, registered, and certified; or b) Class of certified seed that generally is produced from a planting of registered seed, but which also may be produced from foundation or certified seed.

Confined field trial: Field trial containing regulated or stewarded plant materials conducted under conditions that may include requirements for reproductive isolation, site monitoring, plant material/grain disposition, and post-harvest land use restrictions.

Confinement: Practices for field activities where viable seed or vegetative propagating material is planted in the field and managed in a manner that mitigates the spread of pollen, seed, or other propagative plant parts out of the confined field trial area.

Construct: An engineered chimeric DNA designed to be transferred into a cell or tissue; may be synonymous with vector fragment or vector. Typically, the construct comprises the

gene or genes of interest, a marker gene, and appropriate control sequences as a single package.

Containment: The control of viable seed, pollen, or vegetative propagating material in a manner that mitigates their release outside of their controlled development in the laboratory, greenhouse, seed-conditioning, or storage facilities.

Containment facility: Any facility designed to control viable seed, pollen, or vegetative propagating material in a manner that mitigates their release outside of their controlled development in the laboratory, greenhouse, seed-conditioning, or storage facilities.

Critical Control Point: Specific to this Guide, a step at which control can be applied and is essential to prevent, eliminate, or reduce risks to an acceptable level from an activity that may compromise plant product integrity.

Cultivar: Plants within a species bred for distinct characteristics, sometimes called a variety.

Disposition: Describes what was done with the plant material (e.g., planted, destroyed, devitalized, buried, stored, sold, cultured, processed for analysis, or manufactured).

Documentation: Recorded information such as specifications, quality manuals, quality plans, records, and procedure documents.

Documented Information: Standard operating procedures (SOPs), work instructions, forms, records, etc.

Elite germplasm: Plant materials of proven genetic utility, including existing germplasm in commerce or in an advanced stage of development.

Event: A genotype produced from a single transformation of a plant species using a specific genetic construct. For example, two lines of the same plant species that are transformed with the same or different constructs constitute two events.

Event purity: (See **Trait Purity**)

Facility: Sites that are contiguous, under common control by a company or individual, and have a grouping of equipment or individuals engaged in a common process.

Foundation Seed: Seed stocks increased from breeder seed or foundation seed, handled to maintain specific genetic identity and purity. Foundation seed is the source of certified seed, either directly or through registered seed.

Gene: The fundamental physical and functional unit of heredity. A gene is typically a sequence of DNA that encodes a specific functional product (such as a protein or RNA molecule).

Germplasm: The genetic makeup or genome of an individual, group of individuals, or a clone representing a genotype, variety, species, or culture, held in an *in situ* or *ex situ* collection.

Host material: The plant receiving the genetic elements of the construct or the genotype receiving the genetic elements of the construct.

Identity confirmation: For the purposes of this Guide and unless otherwise indicated, identity confirmation may be achieved using either or both of the following:

- Procedural confirmation (e.g., documentation, phenotypic evaluations)
- Analytical confirmation (e.g., laboratory assays)

This will be determined based on individual circumstances and may warrant a case-by-case assessment. It is noted that while phenotypic evaluations can be conducted (e.g., phenological verification involving application of herbicides to verify herbicide tolerance), prudence should be exercised with these methods since results will not be specific to one event (not event specific). Moreover, as technology develops, further additional acceptable confirmation measures maybe develop.

Introgression: The process in plant breeding when genetic information is incorporated into germplasm using traditional plant breeding and backcrossing methods.

Labeling: To affix with a label that is marked with a name and/or other identifying information (e.g., bar code) that can be used to confirm construct or transformant identity.

Line: A group of individuals derived by descent from a single individual within a species.

Low-level presence: Unintentional, trace amounts of biotechnology-derived trait(s) in seed, grain, or food product authorized in one or more countries, but not yet authorized in the country of import.

Phenotypical evaluation: (See **Identity Confirmation**)

Plant: This document defines plant as any plant (including plant part) for or capable of propagation. Various references are made to seed or seed production methods and crop management. It is recognized that systems exist where plant production may be accomplished through non-seed-based methods such as vegetative propagation, and therefore the use of the term "seed" is not meant to limit the scope of this document.

Plant product integrity: Specific to this Guide, plant product integrity (PPI) is the specific identity of a plant and purity of populations of the plant that are established and maintained using appropriate measures.

Product discontinuation: Removal of authorized commercial biotechnology-derived products that have reached the end of their commercial life cycle from the market by the technology owner and not as part of a product recall or withdrawal.

Product launch: The introduction of an authorized biotechnology-derived plant product into commerce.

Product withdrawal: Recovery of product from the supply chain and/or commerce.

Quality Management System (QMS): A component of stewardship, which comprises the processes and systems to establish and maintain quality in each phase of the product life cycle.

Regeneration: The process of growing plant cells, tissues, organs, or an entire plant from a single cell or groups of cells.

Seed stocks: Seed increased from breeder seed and handled so as to closely maintain the genetic identity and purity of a variety used to eventually produce commercial seed.

Standard Operating Procedure (SOP): An established, written method, or set of methods that describes how to routinely perform a given task.

Stewarded material: In a country of cultivation, material that has received authorization, but is pending authorization from key import countries with functioning regulatory systems and may include identity preserved material (e.g., closed loop). These materials and the activities that may occur involving them also may be referred to as directed use and/or authorized noncommercial.

Stewardship: The responsible management of a product throughout the complete lifecycle: from initial research and discovery, through development and registration, during commercialization, and during post-market activities (discontinuation). In agricultural biotechnology, stewardship includes careful attention procedures to maintain plant product integrity as outlined within this guide.

Traceability: The ability to follow the movement of a biotechnology-derived plant through specified stage(s) of development, production, and distribution of seeds or plants to growers.

Trait: A genetically determined characteristic.

Trait purity: A measure of the extent to which an intended trait(s) or event(s) is present, and an unintended trait(s) or event(s) are absent or within allowable tolerances in a population of plants and seed lot.

Transformant: A cell, cell culture, or regenerated plant into which foreign DNA has been introduced.

Transformation: The process of incorporating DNA into an organism's genome. There are several methods to do this in plants. The most commonly used methods for plant transformation are *Agrobacterium*-mediated transformation and biolistic transformation.

Transgenic: An organism created using biotechnology methods that has had genes from another organism added to its genome through recombinant DNA techniques.

Transgenic purity: A measure of the extent to which the intended transgene(s) is present and unintended transgenes are absent in plant material.

Unauthorized: Biotechnology-derived plant material or event that has not been authorized by the relevant competent authorities for release into the environment for purpose of cultivation or for use in the food and feed chains. *Note*: Due to the specific application of this term in the Guide, it has been italicized throughout the document.

Unintended release: Any inadvertent release of plant material that is *unauthorized* in the country of cultivation or pending authorization from key import countries with functioning regulatory systems into the environment, human food, or livestock feed chains.

Variety: Subdivision of a species for taxonomic classification. Used interchangeably with the term cultivar to denote a uniform, stable group of individuals that is genetically and possibly morphologically distinct from other groups of individuals in the species.

Vector: A small, self-replicating DNA molecule (plasmid, virus, bacteriophage, or artificial DNA molecule) that can be used to deliver DNA into a cell, bulk up specific DNA to be used in transformation, or to maintain a construct for archival purposes.