excellence through STEWARDSHIP

GUIDE FOR MAINTAINING PLANT PRODUCT INTEGRITY OF BIOTECHNOLOGY-DERIVED PLANT PRODUCTS

DISCLAIMER

The *Guide for Maintaining Plant Product Integrity of Biotechnology-Derived Plant Products* ("Guide") is solely an educational tool and is guidance to assist users in developing and implementing their own organization-specific process for maintaining the integrity of plant biotechnology products.

The Guide is intended to be 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 process 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

This ETS 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 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[2].

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 ETS principles that are applicable across all modules. After this, and to accommodate different business models, the Guide is sectioned into 5 modules that focus on key stages of a product life cycle for biotechnology-derived plant products:

Module 1	Research in the Laboratory
Module 2	Research in Containment Facilities
Module 3	Confined Field Trials
Module 4	Plant and Seed Multiplication
Module 5	Commercial Plant and Seed Distribution

[2] In addition to this Guide, BIO's guidance document *Containment Analysis and Critical Control Point Plan for Production of Plant-Made Pharmaceuticals and Plant-Made Industrial Products* also applies to biotechnology-derived plants used as production platforms for pharmaceutical or industrial products.

ETS 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[3]

The International Organization for Standardization (ISO)[4] family of standards collectively provides a framework that an organization may use to develop, implement, and maintain quality management systems.

[3] 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.
[4] http://www.iso.org/iso/home/about.htm

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.

HACCP[5]

The Hazard Analysis and Critical Control Point (HACCP)[6] 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.

[5] As with ISO, it is not required to be HACCP-certified to successfully complete an ETS Audit.
[6] 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

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[7]

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.

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[8], tracking, and disposition[9] (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).

[7] As with HACCP, it is not required to be GLP-certified to successfully complete an ETS Audit.
[8] 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.
[9] Describes what was done with the plant material (e.g., planted, destroyed, devitalized, buried, stored, sold, cultured, processed for analysis or manufacture).

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.

Examples of Forms

Excellence Through Stewardship members have access to examples of forms that can be customized for documentation of their various processes. For more information, contact info@ets.bio.

Guidance for Using Modules

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 modules that are applicable to its own individual circumstance. Each module covers activities with shared operational and regulatory considerations.

MODULE 1
Research in the Laboratory

Module 1 describes risk assessment, CCPs, and QMS requirements for activities when research in the laboratory is being planned or conducted. This module has two sections: **Construct Development** and **Plant Transformation and Regeneration.**

The four main areas addressed are:

Analyze Product Integrity Concerns

Determine Critical Control Points

Develop, Establish, and Implement Relevant Aspects of QMS

Resources for Research in the Laboratory

The first stages in the development of a biotechnology-derived plant take place in the contained environment of a laboratory and include activities related to construct development, plant transformation, or other targeted genome modification techniques. Government regulations and guidance pertinent to working with recombinant-DNA molecules, microorganisms, and plants should be incorporated into documented information for activities involving research in the laboratory (e.g., standard operating procedures, work instructions, forms, and records).

When working with third parties (e.g., service contractors, research contractors, technology transfer licensees) it is important that agreements include stewardship and quality management provisions to maintain plant product integrity.

CONSTRUCT DEVELOPMENT

The first section in Module 1: Research in the Laboratory involves construct development. In plant biotechnology, the construct used to transform the host plant is typically comprised of one or more genes of interest (and often a marker gene) coupled with specific regulating elements (e.g., promoters, terminators, transit peptides). It is a customary practice to identify or confirm the identity of the coding and non-coding sequences that will be inserted into the host genome. Selection criteria such as registrability and societal concerns (e.g., toxicity, allergenicity, antibiotic resistance) should be established and considered when selecting the coding sequences and gene regulatory elements.

Analyze Product Integrity Concerns

Consider controls to prevent the following types of errors involving product integrity during activities involving construct development:

- Errors in construct development
- Misidentification of construct
- Mislabeling (e.g., construct, line, batch)
- Errors in tracking or disposition (e.g., constructs, line, batch)

Determine Critical Control Points

- Design and creation of constructs with appropriate genetic elements
- Confirmation of content and organization of constructs
- Transfer of constructs to plant transformation

Develop, Establish, and Implement

Preventive Measures

- Processes for the design of the construct prior to production

- 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)

- Labeling, tracking, and disposition as part of an inventory system for constructs

- Procedures so that labels used to identify a construct are recorded and information pertinent to the construct's identity is retrievable

- Internal work processes and documented information for traceability

Monitoring and Verification Procedures

- Verify the integrity of the construct as designed

- Confirm identity prior to transfer for plant transformation

Corrective Measures

- If 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

- Incorporate any corrective measures or procedural changes into work processes and documented information

- Train personnel on the procedural changes incorporated

Record Keeping and Documentation Procedures

- Documentation of identity and traceability should be secure, accessible, and retained

- 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

The second section in Module 1: Research in the Laboratory involves plant transformation and regeneration. This includes the introduction of constructs by transgenesis into plant cells and *in vitro* regeneration of plants.

Analyze Product Integrity Concerns

Consider controls to prevent the following types of errors involving product integrity during plant transformation and regeneration:

- Misidentification
- Mislabeling
- Errors in tracking
- Errors in disposition
- Errors in devitalization/destruction of GM seed/plant tissue for cancelled or concluded projects

Determine Critical Control Points

- Confirm:
    - Construct identity prior to transformation
    - Host material identity prior to transformation
    - Identity of transformant throughout steps to regenerate plant
- Storage, transfer, and disposition of regenerated plants (e.g., containment growth chamber/greenhouse, or third party)

Develop, Establish, and Implement

Preventive Measures

- Labeling, tracking, and disposition as part of an inventory system for transformants (events)
- Procedures so that labels used to identify host material and transformants are recorded and information pertinent to identity is retrievable
- Internal work processes and documented information for traceability

Monitoring and Verification Procedures

- Prior to transformation, confirm identity of transforming DNA, host, and associated material by documentation or confirm using diagnostic methods
- During steps to regenerate plant, confirm identity of transformant by documentation or confirm by diagnostic methods
- Prior to transfer for further propagation, confirm identity of transformant by documentation or confirm by diagnostic methods
- Processes and criteria for the selection of transformants

Corrective Measures

- If 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
- Incorporate any corrective measures or procedural changes into documented information
- Train personnel on procedural changes incorporated

Incident Escalation and Response Procedures

- Procedures in place to report and escalate any incidents of loss of control or containment of GM traits
- Documentation to ensure that personnel are trained on procedures

Record Keeping and Documentation Procedures

- Records of transformation, regeneration, identity, and traceability should be secure, accessible, and retained as appropriate

- Inventory systems should effectively manage traceability of all materials identification, labeling, tracking, and disposition (e.g., of plasmids, constructs, plantlets, plants, samples, and seed)

- Procedures for the retention of documentation related to nonconformities and follow up actions

Resources for Research in the Laboratory

Regulatory

It is incumbent on each organization undertaking laboratory research with organisms with recombinant DNA to ensure that personnel involved in such research understand all relevant regulatory requirements and related guidance as provided by government regulatory agencies. This information must be incorporated, as appropriate, into an organization's quality management system. Some examples of this type of regulatory guidance include the following:

EC. 1998. Council Directive 98/81/EC of 26 October 1998 amending Directive 90/219/EEC on the contained use of genetically modified microorganisms. Official Journal of the European Communities 5.12.1998 – No L 330 P. 0013 – 0031
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1998L0081:19981205:EN:PDF

EC. 1990. Council Directive 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms. Official Journal of the European Communities - 8.5.90 - Page No L 117/1 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1990:117:0001:0014:EN:PDF

OGTR. 2013. Guidance Notes for the Containment of Exempt Dealings. Office of the Gene Technology Regulator (OGTR), Woden, ACT.
https://www.ogtr.gov.au/resources/publications/guidance-notes-containment-exempt-dealings

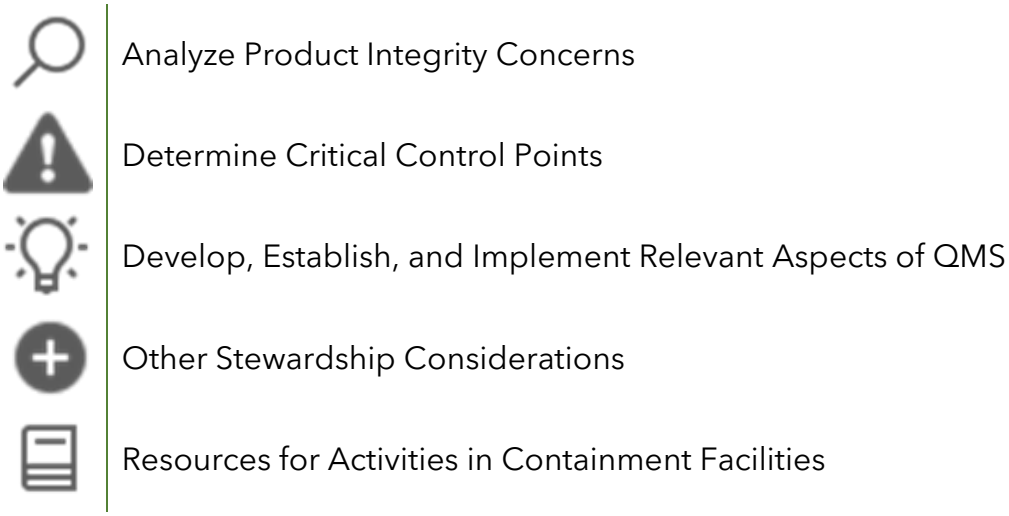
WHO. 2004. Laboratory Biosafety Manual. World Health Organization (WHO), Geneva.
https://www.who.int/publications/i/item/9789240011311

Summary

In summary, Module 1 describes risk assessment, CCPs, and QMS requirements for activities when research in the laboratory is being planned or conducted. The module was split into two sections: Construct Development and Plant Transformation & Regeneration. The main areas addressed include analysis of product integrity concerns; determination of critical control points; development, establishment, and implementation of relevant QMS procedures; and resources for research in the laboratory.

MODULE 2
Research in Containment Facilities

Module 2 describes risk assessment, requirements for CCPs and QMS for activities when research in containment facilities is being planned or conducted. Five main areas are addressed including:



Following plant transformation and the regeneration of whole plants *in vitro* (i.e., event production), the next stage of product development typically takes place in containment facilities such as growth rooms or greenhouses where the initial screening and evaluation of events may take place. This module is directed at working with biotechnology-derived whole plants in such facilities where primary transformants or their derivatives are usually grown for the purposes of early trait evaluation and event screening. Accurate identification of such plants is critical to maintaining plant product integrity during research activities in containment facilities.

When working with third parties (e.g., service contractors, research contractors, technology transfer licensees) it is important that agreements include stewardship and quality management provisions to maintain plant product integrity.

Analyze Product Integrity Concerns

Consider controls to prevent the following types of errors involving product integrity during activities involving research in containment facilities:

- Insufficient isolation or other control measures that do not prevent cross-pollination of plants within the containment facility
- Inadvertent physical mixing of plant material
- Inadequate facilities or controls for containment
- Nonconformance to established seed standards for event purity and impurity
- Misidentification
- Mislabeling
- Errors in tracking
- Errors in disposition

Determine Critical Control Points

- When transferring plant material:
  - To the containment facility
  - Within the containment facility
  - From the containment facility for subsequent propagation
- During contained plant propagation activities:
  - Ensure reproductive isolation within the containment facility
  - Ensure containment measures are maintained and not compromised
  - Measures of control for prevention of inadvertent movement of pollen or seed (e.g., for personnel movement in, out of, or between areas of propagation within containment)

Develop, Establish, and Implement

Preventive Measures

- Space assignment within the facility
- Labeling, tracking, and disposition of propagatable plant material as part of an inventory system
- Procedures so that labels used to identify plants are recorded and information pertinent to identity is retrievable
- Internal work processes and documented information for traceability
- 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)

Monitoring and Verification

- Review space assignment criteria
- Confirm plant identity prior to transfer to, within, or from containment facilities by documentation or verify using diagnostic methods where appropriate
- 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

Corrective Measures

- In the case that 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
- Correct any deficiencies identified that could affect the integrity of the materials or containment facility

- Correct any deficiencies identified that could affect reproductive isolation or appropriate separation of plant material

- Incorporate any corrective measures or procedural changes into documented information

- If applicable, train personnel on the procedural changes incorporated

Incident Escalation and Response Procedures

- Procedures in place to report and escalate any incidents of loss of control or containment of GM traits

- Documentation to ensure that personnel are trained on procedures

Record Keeping and Documentation Procedures

- Documentation of analyses, identity, and traceability should be secure, accessible, and retained, as appropriate

- Procedures for the retention of records related to nonconformities and follow up actions

- Inventory systems should effectively manage traceability of all materials identification, labeling, tracking, and disposition (e.g., of plantlets, plants, samples, and seed)

Other Stewardship Considerations

Prior to the transfer of *unauthorized*[10] plants from a containment facility to the field, evaluate and verify their identity, presence of intended trait(s), and absence of unintended traits (e.g., failure of isolation procedures during pollen flow). Evaluation and verification may include review of records involving handling procedures, or analytical data. To determine an appropriate level of assurance and whether there is a need for additional analytical testing, it is advisable to undertake a case-by-case assessment that may include the following considerations:

Biology of the host plant/breeding protocol: The reproductive biology of the host plant or the breeding protocol used to propagate and select the *unauthorized* plants

[10] *Unauthorized* refers to biotechnology-derived plant material that has not been authorized by the relevant competent regulatory authorities for release into the environment for purpose of cultivation or for use in the food and feed chains.

destined for confined field release may be such that identity and transgenic purity can be confirmed in the absence of any additional testing.

Receiving environment: If the field release is for further propagation (as compared to a terminal study), the location of the confined field trial site and surrounding area may need to be free of any sexually compatible relatives or commercial cultivation of the host plant species in order to reduce concern about potential cross-pollination.

Implications of regulatory requirements: Based on findings from the above, regulations, guidelines, or the confined field trial permit may prescribe the level of testing that must be undertaken to confirm plant identity and transgenic purity prior to field release.

Supplemental Plant Product Integrity Screening: To supplement PPI screening, phenotypic evaluations can be conducted (e.g., phenological verification involving application of herbicides to verify herbicide tolerance). Note: results will not be event specific.

Resources for Activities in Containment Facilities

Regulatory and Other Guidance

Research and other activities undertaken with *unauthorized* plant products of biotechnology in containment growth rooms or greenhouses should be conducted in accordance with government regulations and guidance pertinent to working with recombinant-DNA plants. Examples of such guidance include:

NIH. (2013). NIH Guidelines for Research Involving Recombinant DNA Molecules: Appendix P: Physical and Biological Containment for Recombinant DNA Research Involving Plants. National Institutes of Health (NIH), Bethesda. http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines

OGTR. (2013). Guidelines for Certification of a Physical Containment Level 2 Plant Facility. Office of the Gene Technology Regulator (OGTR), Woden, ACT. https://www.ogtr.gov.au/resources/publications/guidelines-certification-physical-containment-level-1-facility

Traynor, P.L., Adair, D. & Irwin, R. (2001). A Practical Guide to Containment: Greenhouse Research with Transgenic Plants and Microbes. Information Systems for Biotechnology, Virginia Tech, Blacksburg, VA. https://vtechworks.lib.vt.edu/handle/10919/78423

Handbook for Understanding and Implementing the Containment Analysis and Critical Control Point Plan for the Production of Plant-Made Pharmaceuticals and Plant-Made Industrial Products, which is intended for use as a reference document in developing company-specific CACCP plans, detailed operating procedures, and disciplines consistent with their respective plant host production systems.
chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.cbd.int/doc/books/2008/B-03130.pdf

Inspection for Containment Facilities

Frequent, routine, and periodic inspections of the containment facility are recommended to confirm that the appropriate level of containment has been maintained and that features that are designed to maintain confinement have not been compromised. Inspection activities should be documented in accordance with the organization's record keeping and documentation procedures.

Summary

In summary, Module 2 describes risk assessment, requirements for CCPs, and QMS for activities when research in containment facilities is being planned or conducted. Five main areas were addressed including: analysis of product integrity concerns; determination of critical control points; development, establishment, and implementation of relevant QMS procedures; other stewardship considerations; and resources for activities involving research in containment facilities.

MODULE 3
Confined Field Trials

Module 3 describes requirements for CCPs and QMS for activities when confined field trials are being planned or conducted. The four main areas addressed are:


Analyze Product Integrity Concerns


Determine Critical Control Points


Develop, Establish, and Implement Relevant Aspects of QMS


Resources for Confined Field Trials

Within the product life cycle, confined field trials represent the controlled introduction of a biotechnology-derived plant into the environment. As such, these activities are distinctly different from the work performed in containment facilities, such as laboratories, growth chambers, and greenhouses, and from the work associated with seed multiplication or commercial cultivation that occurs after product authorization by regulatory authorities.

Field trials for evaluating efficacy and agronomic performance are critical to product development, whether the product is a biotechnology or non-biotechnology crop. Being able to conduct field trials with biotechnology-derived plants is an essential part of the product development pathway. It provides developers with opportunities to collect data addressing the information requirements established by regulatory authorities for environmental, food, and feed safety assessments in the country of cultivation and key import countries. Confined field trials are generally small in scale. Larger field trials may be necessary to confirm trait and agronomic performance and to produce sufficient material for analytical tests in support of food, feed, and environmental safety evaluations. Confined field trials may be used to produce breeder, basic, or foundation seed in the country of cultivation prior to authorization of the biotechnology-derived plant in key import counties with functioning regulatory systems (see also Module 4).

Events may be selected for introgression of the desired trait(s) into elite germplasm. Introgression is often achieved using conventional plant breeding techniques that are similar to those applied in the development of non-transgenic varieties (e.g., directed and controlled cross-pollination and selection techniques). Breeding into elite germplasm is often initiated before product authorization is received from regulatory agencies, so confinement of breeding nurseries may be necessary. As with any breeding program, it is critical that plant product integrity be maintained including maintenance of purity of the biotechnology-derived event of interest and prevention of impurity (AP, LLP) within the standards determined by an organization, seed association, and/or regulatory governmental authority.

When working with third parties (e.g., service contractors, research contractors, technology transfer licensees) it is important that agreements include stewardship and quality management provisions to maintain plant product integrity during confined field trial activities.

Analyze Product Integrity Concerns

Consider controls to prevent the following types of errors involving product integrity during activities involving confined field trials:

- Insufficient isolation or control of plants to limit out-crossing
- Misidentification and errors in evaluating the transgenic purity of plant material to be planted, harvested, or retained
- Nonconformance to established seed standards for event purity and impurity
- Inadvertent physical mixing or comingling of seed lots in storage or machinery while being transported, cleaned, or processed
- Errors in disposition

Determine Critical Control Points

- Confirm required regulatory documents are in place to allow planting
- Segregation of *unauthorized* plant material from other seed and plant materials

- Assessment of plant material before planting
- Transfer of plant material to the field trial site for planting (includes transfer to intermediate facilities such as field stations prior to planting)
- Confirmation of confinement
- Isolation to prevent inadvertent cross-contamination during pollen flow
- Planting the materials
- Harvesting the seed, grain, or plant product
- Processing seed, grain, or plant product
- Transfer of plant material from the field trial site
- Storage of harvested material
- Use of harvested material in country of cultivation
- Material disposition

Develop, Establish, and Implement

Preventive Measures

- A procedure for site selection and planning for the controlled environmental release
- Labeling, tracking, and disposition of plant material as part of an inventory system
- Procedures to ensure that labels used to identify plants or seeds are recorded and information pertinent to identity is retrievable
- Internal work processes and documented information for traceability

- Transfer protocols or processes for traceability across functions, departments, organizations, or locations

- 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)

- 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)

- 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)

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

- 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

Monitoring and Verification Procedures

- Confirm:
  - Plant identity prior to transfer to the field trial site

  - Plant identity and assessment of transgenic purity of plant material from the trial site by documentation or by using diagnostic methods where appropriate

  - Confinement measures through assessment

- 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

- Volunteer monitoring

Corrective Measures

- 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

- Correct any deficiencies that could affect confinement of the field trial site and assess impact on plant product integrity

- Incorporate any corrective measures or procedural changes into the SOP, as appropriate

- If applicable, train personnel on the procedural changes incorporated

- Incorporate reporting and resolution procedures for potential regulatory compliance incidents

Incident Escalation and Response Procedures

- Develop, Establish, and Implement an incident response procedure (refer to *Guide for Incident Response*)

- Procedures in place to report and escalate any incidents of loss of control or confinement of GM traits

- Documentation to ensure that personnel are trained on procedures

- Ensure corrective actions are taken and documented. If applicable, report incident to appropriate regulatory authorities

Record Keeping and Documentation Procedures

- Documentation of trial conduct, identity and traceability should be secure, accessible, and retained as appropriate

- 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

- Procedures for the retention of documentation related to nonconformities and follow up actions

- 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

- Inventory systems should effectively manage traceability of all materials identification, labeling, tracking, and disposition (e.g., plants, samples, and seed)

Resources for Confined Field Trials

Regulatory and Other Guidance

Management of a confined field trial requires a significant commitment to meet the terms and conditions of authorization of the trial by regulatory authorities. The commitment must continue throughout the trial, at harvest, and any prescribed period of monitoring or post-harvest land-use restriction. Most regulatory authorities have published regulations and supporting guidance for the management of confined field trials. Some examples include:

Brazil – National Technical Committee for Biosafety

http://ctnbio.mctic.gov.br/inicio

South Africa – GMO Activities

https://www.gov.za/services/plant-production/gmo-activities

India – Review Committee on Genetic Manipulation Knowledge Portal

https://ibkp.dbtindia.gov.in/

United States – USDA/APHIS- SECURE Rule

https://www.aphis.usda.gov/biotechnology/regulations/secure-rule

In addition, the Biotechnology Innovation Organization (BIO) has developed educational tools to assist users in better understanding and meeting the

management responsibilities associated with conducting confined field trials in the United States:

> *Regulatory Guidelines During Confined Field Trials of Biotech Crops*, which provides information about notification and permitting procedures; compliance and enforcement; transport and storage; trial site management; harvest disposition; post-harvest management; audit and verification; and experimental use permits for plant-incorporated protectants. https://croplife.org/wp-content/uploads/2014/04/Compliance-Management-of-confined-field-trials-of-bio-derived-plants.pdf

Other resources that address the management of confined field trials include:

> CropLife International. (2010). *Compliance Management of Confined Field Trials for Biotech-Derived Plants.* CropLife International, Brussels. https://croplife.org/wp-content/uploads/2014/04/Compliance-Management-of-confined-field-trials-of-bio-derived-plants.pdf

Summary

In summary, Module 3 describes requirements for CCPs and QMS for activities when confined field trials are being planned or conducted. Four main areas were addressed including: analysis of product integrity concerns; determination of critical control points; development, establishment, and implementation of relevant aspects of QMS; and resources for confined field trial activities.

MODULE 4
Plant and Seed Multiplication

Module 4 describes requirements for CCPs and QMS for activities when plant and seed multiplication is being planned or conducted. Four main areas are addressed including:


Analyze Product Integrity Concerns


Determine Critical Control Points


Develop, Establish, and Implement Relevant Aspects of QMS


Resources for Plant and Seed Multiplication

Plant and seed multiplication is the continuous process in which plant products are grown according to defined standards and requirements to ensure genetic identity, maintain varietal purity, and meet certain quality standards before distribution to growers. In many countries, seed multiplication is part of a legally sanctioned system for quality control of seed production. Organizations often manage several classes of seed during plant and seed multiplication, and classes of seed may be defined by regulatory authorities at local, state, and/or federal levels where seed registration and certification are involved (e.g., breeder seed, foundation seed, registered seed, and certified seed). These seed classes are synonymous with OECD Seed Schema: Pre-Basic (breeder seed), Basic (Foundation/Registered seed), and Certified seed. In countries that do not require formal registration and certification, an organization often defines the classes of seed that are managed during plant and seed multiplication and the actions taken at critical control points for each seed class to ensure plant product integrity.

When working with third parties (e.g., service contractors, research contractors, technology transfer licensees) it is important that agreements include stewardship and quality management provisions to maintain plant product integrity during plant and seed multiplication.

When plant and seed multiplication of a particular biotechnology-derived plant and related trait is authorized in the country of cultivation prior to import authorizations in key countries of import with functioning regulatory systems, the production plots need to be managed similar to confined trials[11], and the derived seed or plants need to be handled as *unauthorized* material (see Module 3) or appropriately channeled to avoid trade disruptions. This category of material, the associated activities, and commodities produced may be referred to as stewarded, directed use, and/or authorized non-commercial activities.

Analyze Product Integrity Concerns

Consider controls to prevent the following types of errors involving product integrity during plant and seed multiplication:

- Insufficient isolation of plants that does not prevent unintended outcrossing
- Misidentification of plant material to be planted
- Misidentification of plant material harvested and retained
- Nonconformance to established seed standards for event purity and impurity
- Inadvertent physical mixture of plant material (e.g., due to incomplete clean-out of planting, harvesting, transporting, and conveying equipment, or within storage facilities)
- Isolation distances to help address outcrossing and in-crossing concerns.
- Errors in disposition

Determine Critical Control Points

- Seed packaging, storage, and preparation of plant material for planting
- Transfer of plant material to the field for planting
- Confirmation of reproductive isolation, as necessary

[11] In the United States, all seed production prior to commercial authorization must be done under a USDA permit or notification, and when applicable, EPA authorization in the context of a confined field trial.

- Plant pollination, harvesting, crop destruction, and post-harvest monitoring, as necessary
- Transfer of plant material from the field for cleaning, conditioning, packaging, storage, or transport
- Disposal of regulated/stewarded treated seed
- Storage
- Alternative uses for grain if key import authorizations have not been received (e.g., feed on farm, ethanol production)

Develop, Establish, and Implement

Preventive Measures

- Effective processes and procedures supported by robust training
- Quality assurance and control processes to ensure seeds are properly tested and that results are recorded
- Labeling, tracking, and disposition of plant material as part of an inventory system
- Procedures so that labels used to identify seeds or plants are recorded and information pertinent to identity is retrievable
- Internal work processes and documented information for traceability
- Transfer protocols or processes for traceability across functions, departments, organizations, or locations
- Methods and controls for reproductive isolation, as necessary (e.g., compliance with national standards for production of breeder, foundation, registered, and certified seed)
- Methods and controls for appropriate equipment cleaning and sanitation

- Methods and controls for appropriate seed storage, shipment, and disposal

- Training for individuals involved with activities related to plant and seed multiplication, including where these are managed within confined field trials, if applicable

Monitoring and Verification Procedures

- Confirm:
    - Seed or plant identity prior to transfer of seed or plant material to the field

    - 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)

    - Develop, Establish, and Implement methods and controls for appropriate post-harvest monitoring requirements

    - Seed or plant identity during storage or shipment

- 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)

Corrective Measures

- 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

- Correct any deficiencies identified that could affect the reproductive isolation of the field sites and assess impact on plant product integrity

- Incorporate any corrective measures or procedural changes into documented information as appropriate and ensure relevant personnel are trained

Incident Escalation and Response Procedures

- Develop, Establish, and Implement appropriate incident response protocols to ensure timely and accurate reporting of corrective actions (refer to *Guide for Incident Response*)

- Procedures in place to report and escalate any incidents of loss of control of GM traits

- Documentation to ensure that personnel are trained on procedures

Record Keeping and Documentation Procedures

- Records of production, identity, and traceability should be secure, accessible, and retained as appropriate

- Procedures for the retention of records related to nonconformities and follow up actions

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

Resources for Plant and Seed Multiplication

International Seed Testing Association[12]

The International Seed Testing Association (ISTA) works to develop, adopt, and publish internationally agreed standard procedures (Rules) for sampling and testing seeds to facilitate international trade and award accreditation to laboratories.

- ISTA International Rules for Seed Testing – globally available and annually updated, harmonized, uniform seed testing methods

- ISTA Accreditation Program, including Accreditation Standard, Proficiency Testing and Auditing Program, to assist in ensuring worldwide, harmonized, uniform seed testing

[12] https://www.seedtest.org/upload/cms/user/ISTAAccreditationStandardforSeedTestingandSeedSamplingV6.111.pdf

Summary

In summary, Module 4 describes requirements for CCPs and QMS for activities when plant and seed multiplication is being planned or conducted. Four main areas were addressed including: analysis of product integrity concerns; determination of critical control points; development, establishment, and implementation of relevant aspects of QMS; and resources.

MODULE 5
Commercial Plant & Seed Distribution

Module 5 describes requirements for CCPs and QMS for activities when commercial plant and seed distribution are being planned or conducted. Three main areas are addressed including:


Analyze Product Integrity Concerns


Determine Critical Control Points


Develop, Establish, and Implement Relevant Aspects of QMS

Maintaining plant product integrity remains important in commercial seed because regulatory authorizations may not be granted at the same time in all countries. Prior to the commercial introduction or distribution of any biotechnology-derived plant or seed, the product developer or its licensee should have obtained all necessary regulatory authorizations as a prerequisite to market launch in a manner consistent with the *Guide for Product Launch Stewardship*. These may include environmental, food, and feed safety authorizations, as well as any other requirements under national seed and/or phytosanitary regulations. If the product is intended for food or feed use, plan to make an appropriate detection method or test commercially available to confirm plant product integrity.

The entire distribution channel for a biotechnology-derived plant product is often not controlled by one entity; but rather by several entities involved with production, storage, conditioning, processing, sales, and distribution to customers. Therefore, a single entity will not likely be involved in all steps of the production and distribution process for biotechnology-derived plant products. However, each entity is responsible for those steps that are within its scope of operation.

This module provides guidance for developers, producers, licensees, and distributors of biotechnology-derived plant or seed products for activities associated with the introduction or distribution of biotechnology-derived plant or seed products into

commercial distribution channels and markets. The scope of this module includes activities to process, condition, treat, store, and package products resulting from seed and plant multiplication. Other activities potentially covered in this module include determining purity of the seed lot, the movement or transport of materials from production or processing locations to and from subsequent processing or storage locations prior to commercial distribution, and storage and control of products and inventory in various stages of processing and packaging prior to commercial distribution. The final activities covered include the transport of finished products to commercial points-of-sale for subsequent sale and distribution, and the distribution of products through markets to customers.

When working with third parties during activities involving commercial plant and seed distribution (e.g., service contractors, technology transfer licensees), it is important that agreements include stewardship and quality management provisions to maintain plant product integrity.

Analyze Product Integrity Concerns

Consider controls to prevent the following types of errors involving product integrity during commercial plant and seed distribution:

- Errors in product identity
- Errors in trait purity
- Nonconformance to established seed standards for event purity and impurity
- Presence of unintended traits
- Inadvertent physical mixture of plant material

Determine Critical Control Points

- Transfer and labeling of plant materials for cleaning, conditioning, packaging, storage, and/or transport within the organization
- Transfer and labeling of plant materials for cleaning, conditioning, packaging, storage, and/or transport to interim or final destinations external to the organization

- Order entry and fulfillment for materials to be distributed

Develop, Establish, and Implement

Preventive Measures

- Define appropriate seed quality standards to be achieved in order that plants/seeds are suitable for their intended use

- Implement an appropriate quality control strategy to ascertain seed quality standards are being fulfilled

- Labeling, tracking, and disposition of plant material as part of an inventory system for activities up to and including the point of commercial distribution

- Procedures so that information used to identify plant products is recorded on labels and associated with documentation pertinent to identity and production history

- Internal work processes and documented information for traceability

- Transfer protocols or processes for traceability across functions, departments, organizations, and locations

- Protocols and processes for equipment cleaning and inspection to avoid inadvertent physical mixture (dedicated equipment should be considered where appropriate)

- Seed processing, warehousing, and distribution processes to maintain plant product integrity and avoid inadvertent physical mixture

Monitoring and Verification Procedures

- Confirm plant identity prior to cleaning, packaging, and transport by documentation or verify using diagnostic methods where appropriate

- Verify that the plant product meets the quality standard for intended use

Corrective Measures

- Develop, establish, and implement processes for product containment, withdrawal, and recall

- If 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

- Develop, establish, and implement processes for receiving, controlling, and determining the disposition of returned materials

- Incorporate procedural changes into standard operating procedures and train relevant personnel to prevent recurrence of nonconformities

Incident Escalation and Response Procedures

- Procedures in place to report and escalate any incidents of loss of control of GM traits

- Documentation to ensure that personnel are trained on procedures

- Incorporate appropriate incident response protocols to ensure timely and accurate reporting of corrective actions

Record Keeping and Documentation Procedures

- Procedures so that documentation of production, processing, distribution, identity, and traceability is secure, accessible, and retained as appropriate

- Procedures for the retention of documentation related to nonconformities and follow up actions

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

Summary

In summary, Module 5 describes requirements for CCPs and QMS for activities when commercial plant and seed distribution are being planned or conducted. Three main areas were addressed including: analysis of product integrity concerns; determination of critical control points; and development, establishment, and implementation of relevant aspects of QMS.

Guide Summary

This 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 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 ETS members establish procedures based on the content of this ETS Guide for each relevant stage of their product life cycle for biotechnology-derived plant products.

Abbreviations/Acronyms

AP	Adventitious Presence
BIO	Biotechnology Innovation Organization
BQMS	Biotechnology Quality Management System Program
CACCP	Containment Analysis and Critical Control Point
CCP	Critical Control Point
CCPs	Critical Control Points
DNA	Deoxyribonucleic acid
ETS	Excellence Through Stewardship
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**)

Biotechnology Quality Management Support Program: A voluntary program developed by the United States Department of Agriculture that was intended to assist organizations involved in biotechnology research and development, (including small businesses and academic researchers), analyze the critical control points within their management systems to better maintain compliance with the APHIS regulations (7 CFR part 340) for the import, interstate movement, and field release of regulated, genetically engineered organisms.

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.

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