EXCELLENCE THROUGH STEWARDSHIP®

Advancing Best Practices in Agricultural Biotechnology

GUIDE FOR

Maintaining Plant Product Integrity

OF

Biotechnology-Derived Plant Products

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 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

Purpose

This Guide provides information on how to develop and implement a stewardship program and quality management system that will assist product developers in maintaining plant product integrity from research and discovery through commercialization and post-market activities[1]. 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[2] can have serious consequences for a product developer and commercial trade.

The Guide has been developed as a series of informative educational modules that can be adapted to the specific activities pertinent to the user's own operations, including incorporation into existing quality management systems. Common to all of the modules is an emphasis on the importance of product identification and traceability as well as documentation and data governance.

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. However, it is recognized that there are techniques other than transformation that can be used to alter the plant's genome such as the use of precise genome modification techniques that can add to, edit, or delete the plant's own DNA. It is important to note that the products derived from these alternate methods may be regulated similar to transformation products in some countries and not in others (e.g., the process by which the biotechnology plant is derived is the regulatory trigger in the United States versus the novelty of the product itself is the trigger for regulation in Canada). Therefore, while some of the modules within this document provide greater detail on plant transformation, the principles and protocols for developing and implementing a product stewardship program for plants derived from other methods of genome modification are similar. Thus, the modules are

[1] These include product discontinuation and incident response.

[2] Examples of material out of place include adventitious presence (AP) and low-level presence (LLP). AP is the unintentional and incidental presence of trace amounts of biotechnology-derived trait(s) in seed, grain or food product. LLP is a type of AP where the presence of unintentional, trace amounts of biotechnology-derived trait(s) authorized in one or more country(ies) are detected in the country of import prior to authorization in that country. 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.

applicable and can be utilized with appropriate modification based on the method of genome modification.

Scope

This Guide addresses quality management systems for the full life cycle of plant[3] products to address biotechnology-derived[4] traits that could be present in food, feed or the environment (i.e., cultivation). It is applicable to all stages of the plant product life cycle from initial research and discovery through development and registration to commercialization and post-market activities[5].

[3] This document defines plant as any plant (including plant part) for or capable of propagation. Various references are made to seed and/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.

[4] The Convention on Biological Diversity defines biotechnology "as 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.

[5] 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.

Supporting Documents

BIO. 2010. Regulatory Guidelines During Confined Field Trials of Biotech Crops. Biotechnology Industry Organization (BIO), Washington DC. http://www.bio.org/articles/regulatory-guidelines-during-field-trials-biotech-crops

BIO. 2008. Handbook for Understanding and Implementing the Containment Analysis and Critical Control Point Plan for Production of Plant-Made Pharmaceuticals and Plant-Made Industrial Products. Biotechnology Industry Organization (BIO), Washington DC. http://www3.bio.org/foodag/plants/BIO_CACCP_2007.pdf

BQMS. 2011. Biotechnology Quality Management System (BQMS) Program. United States Department of Agriculture (USDA), Washington DC. http://www.aphis.usda.gov/biotechnology/bqms_main.shtml

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

ISO. 2011. Guidelines for quality and/or environmental management systems auditing (ISO 19011:2011). International Organization for Standardization (ISO), Geneva. http://www.iso.org/iso/catalogue_detail?csnumber=31169

ISO. 2008. Quality management systems – Requirements. (ISO 9001:2008). International Organization for Standardization (ISO), Geneva. http://www.iso.org/iso/home/standards/management-standards/iso_9000.htm

ISO. 2005. Quality management systems – Fundamentals and vocabulary (ISO 9000:2005). International Organization for Standardization (ISO), Geneva. http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=42180

Acronyms

AP	Adventitious presence
BIO	Biotechnology Industry Organization
BQMS	Biotechnology Quality Management System Program
CACCP	Containment Analysis and Critical Control Point
CCP	Critical Control Point
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: 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.

Biotechnology Quality Management System Program: A voluntary program developed by the United Stated Department of Agriculture that is 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: Seed or vegetative propagating material, increased by the originating, sponsoring plant breeder or institution, used as the first source 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: The control of viable seed or vegetative propagating material planted in the field in a manner that mitigates the spread of pollen or other propagative plant parts out of the confined 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 limit access by unauthorized personnel as well as egress of controlled plant materials.

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: The act or means of settlement of (i.e., what was done with) plant material (e.g., planted, devitalized, buried, stored).

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

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.

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.

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

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.

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.

Regeneration: The process of growing plant cells 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 render 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).

Stewardship: Product stewardship is the responsible management of a product from its inception through to its ultimate end and discontinuation. In agricultural biotechnology,

stewardship includes careful attention to the safety of products and their market impact is essential for high value products in any industry.

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 the intended trait(s) is present and unintended traits are absent in a population of plants.

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.

Background

Quality Management Systems

This section provides considerations for the implementation of a process-based quality management system (QMS). Quality Management consists of the systems and processes needed to establish stewardship and maintain quality in each phase of the product life cycle tailored to the type and scope of operations for your organization. For the discussion of implementing a QMS, we will use the International Organization for Standardization (ISO)[6] family of standards as an example. An organization is not required to be ISO-certified to participate in ETS, but must have a functional QMS.

The ISO family of standards collectively provides a framework that an organization may use to develop, implement, and maintain a management system that incorporates a process for continual performance improvement while addressing the needs of interested parties. In the case of biotechnology-derived plants, "interested parties" may include regulators, growers, and other members of the value chain whose business interests may be affected by the development and commercialization of transgenic plants. ISO identifies eight 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:

1. Customer focus

Organizations depend on their customers. Therefore, they should understand current and future customer needs; they should meet customer requirements; and they should strive to exceed customer expectations.

2. Leadership

Leaders establish unity of purpose and the direction of the organization. They should create and maintain the internal environment in which people can become fully involved in achieving the organization's objectives.

3. Involvement of people

People at all levels are the essence of an organization. Their full involvement enables their abilities to be used for the organization's benefit.

4. Process approach

A desired result is achieved more efficiently when activities and related resources are managed as a process.

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

5. System approach to management

Identifying, understanding, and managing interrelated processes as a system contributes to the effectiveness and efficiency with which an organization achieves its objectives.

6. Continual improvement

Continual improvement of the organization's overall performance should be a permanent objective of the organization.

7. Factual approach to decision making

Effective decisions are based on the analysis of data and information.

8. Mutually beneficial supplier relationships

An organization and its suppliers are interdependent, and a mutually beneficial relationship enhances the ability of both to create value.

The requirements for quality management systems as specified in ISO 9001:2008 are purposefully generic so that they may be applied by any organization that wishes to establish a quality management system irrespective of the product or service that the organization may offer. Product- or service-specific requirements can be specified by the organization in response to perceived or actual needs of interested parties. Such requirements may be indicated in, for example, policies, SOPs, contractual agreements, and regulatory requirements.

Developing and implementing a documented quality management system consists of multiple steps as described below. These steps have been incorporated as the foundation for this Guide[7] and include the following:

- Determining the needs and expectations of customers and other interested parties
- Establishing the quality policy and quality objectives of the organization
- Determining the processes and responsibilities necessary to attain the quality objectives
- Determining and providing the resources necessary to attain the quality objectives
- Establishing procedures and methods to measure the effectiveness and efficiency of each process
- Applying these measures to determine the effectiveness and efficiency of each process
- Determining means for preventing non-conformities and eliminating their causes

[7] This does not imply that this Guide is compliant with ISO.

- Establishing and applying a process for continual improvement of the quality management system

When developing a quality management system, an organization must identify and manage a series of interrelated or linked activities. According to ISO 9001:2008, an activity that uses resources and is managed in a manner directed to enabling the transformation of inputs into outputs can be considered as a process.

The application of a system of processes within an organization, together with the identification and interactions of those processes and their management, is referred to in ISO 9001:2008 as the “process approach,” which emphasizes the importance of the following objectives:

- Understanding and meeting requirements
- Considering processes in terms of added value
- Obtaining results of process performance and effectiveness
- Continuing to improve processes based on objective measurement

The linkages between processes can be seen when the output from one process forms an input for the next process. The various activities that span the life cycle of a biotechnology-derived plant from product development to commercial sales and, ultimately, product discontinuation are a series of interlinked processes that collectively make up the “system” that is to be managed with respect to the quality of plant product integrity.

The following provides an example of processes that could collectively form a quality management system for plant product integrity applicable across the product life cycle—from research and development in the laboratory, through testing, to commercial distribution and, finally, product discontinuation. Depending on the needs and size of an organization, those processes may be addressed at the management and functional, and/or operational levels:

- Documentation: Processes to manage and control quality system documentation and the records generated by the quality management system. Documentation (e.g., specifications, quality manuals, quality plans, records, or procedure documents) may be in printed, electronic, video, or other media. The aim is to have documentation that is relevant and readable; controlled to maintain content integrity; clearly and consistently identified; deployed to all users; reviewed in a timely manner; retrievable; and maintained according to an organization’s record management policy.

- Addressing non-conformance: A process for responding to non-conformities

(e.g., non-conforming product, unintended release of product, or product recall) including establishing corrective and preventive actions.

- Management and compliance reviews: A process by which management monitors and addresses changes to the quality management system.

- Product identification and traceability: Processes to name and identify plant material[8], track plant material used for propagation as it moves between facilities and field, and track disposition of plant material.

- Training and competency: A process to define training requirements and standards so that effective training can be implemented and monitored through auditing and competency assessment.

- Continuous program improvement: A process to use the results of activities such as management reviews, audits, and compliance reviews to improve the effectiveness of the quality management system.

- Auditing and compliance: Processes for monitoring, measuring, and auditing the quality management system, including defining audit criteria, scope, frequency, and methods for internal and third-party audits.

[8] Misunderstandings can arise when a single event is named or described differently by product developers or regulatory authorities in different countries. To address the confusion this can cause, the Organization for Economic Co-operation and Development (OECD) has published *Guidance for the Designation of a Unique Identifier for Transgenic Plants* (see http://www.oecd.org/science/biotrack/46815728.pdf). The OECD Unique Identifier is a nine-digit alphanumeric code that is given to each genetically engineered plant that is authorized for commercial use, including planting and food/feed use. Product developers can generate an identifier and include it in the dossiers that they forward to national authorities during the safety assessment process. Once authorized, national authorities can then forward the unique identifier to the OECD Secretariat for inclusion in the OECD's product database.

Hazard Analysis and Critical Control Point (HACCP)

The HACCP system is an internationally-accepted approach to ensuring food safety. It is applied throughout the food chain from primary production to consumption of the food product. It is used as a science-based and systematic tool to assess hazards and establish control systems that focus on prevention rather than relying mainly on end-product testing[9]. According to *Codex Alimentarius* "the application of HACCP is compatible with the implementation of quality management systems, such as the ISO 9000 series, and is the system of choice in the management of food safety within such systems[10]."

The HACCP system consists of the seven principles listed below, applied in a logical sequence. These principles have been used to assist in the preparation of this Guide.

Principle 1: Conduct a hazard analysis.

Principle 2: Determine the Critical Control Points (CCPs).

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.

[9] 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

[10] *Ibid*

Format of this Guide

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. To accommodate these different business models, this Guide has been prepared in a modular fashion. The organization can adopt the modules that are applicable to its own individual circumstance. Each module covers activities with shared operational and regulatory considerations. The HACCP principles have been applied to these activities, particularly to assist in the identification of CCP where interventions are considered necessary to confirm product integrity (see Figures 1a and 1b). The critical control points outlined in each of the modules should be assessed in the development and operation of a quality management system. The selection and extent of the preventive measures for each of the identified control points should be determined by taking into account the nature of the process or product and associated aggregate controls. The extent and application of these measures should be justified.

Figure 1a

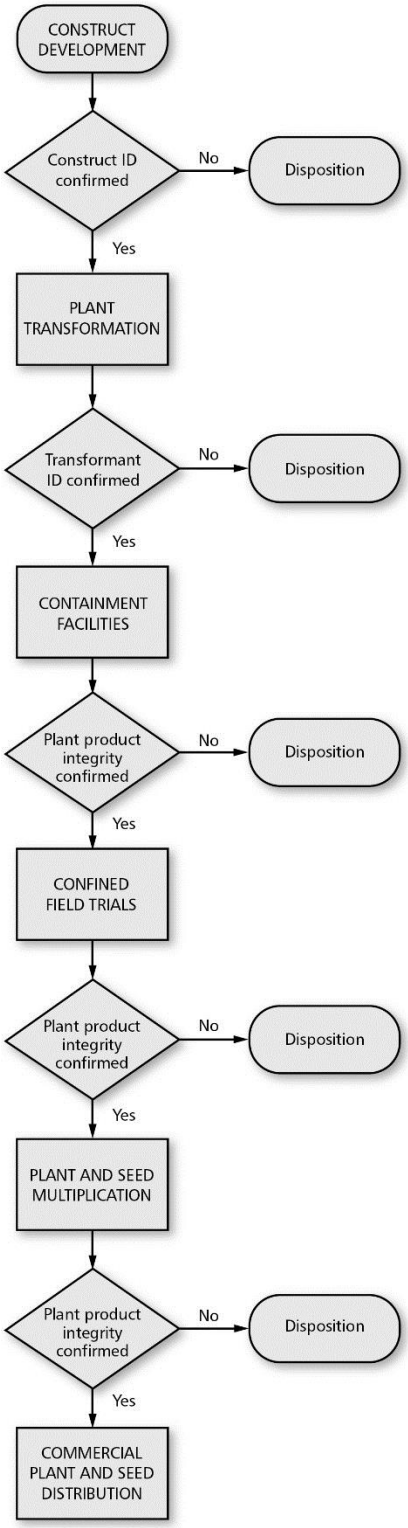
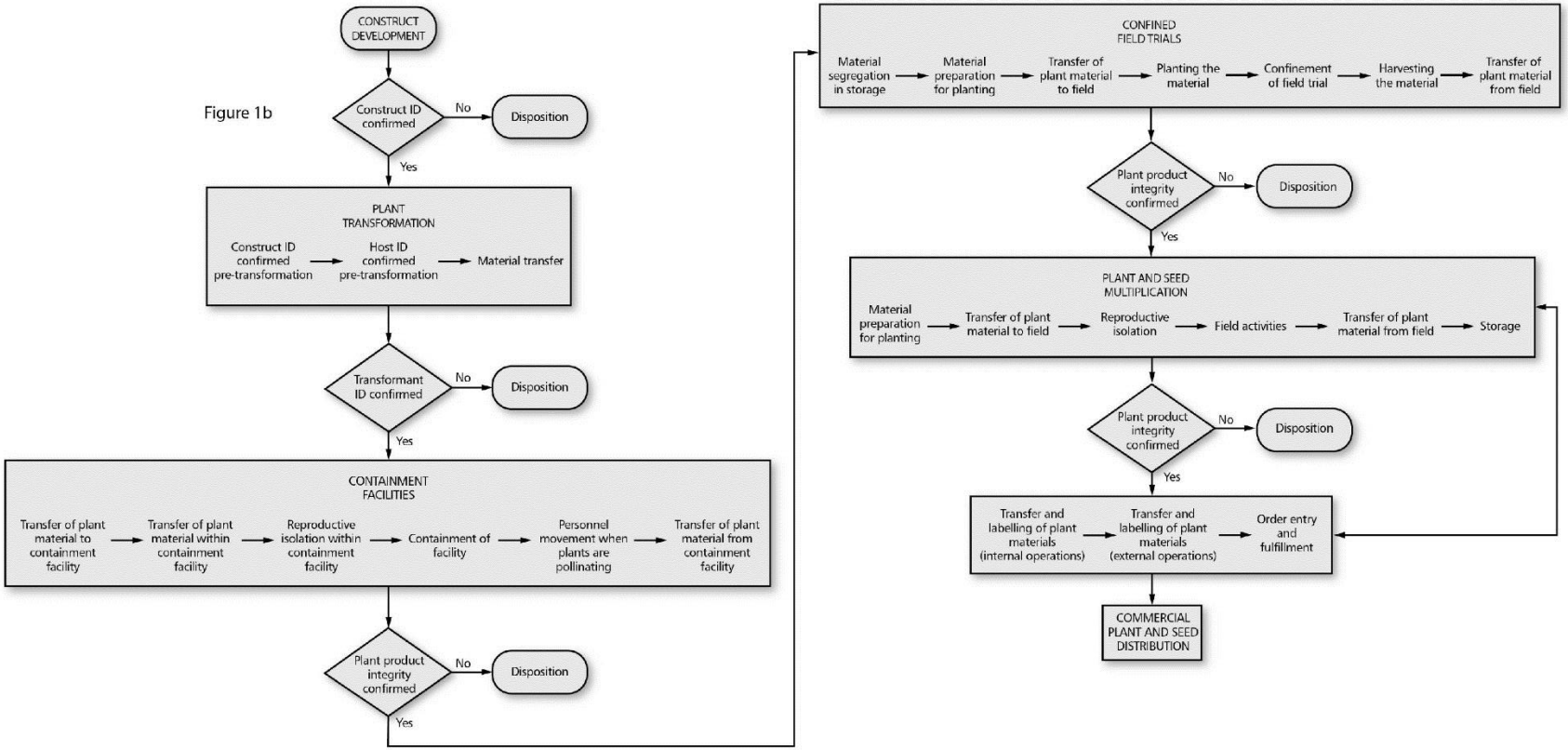


FIGURE 1. Work flow diagram indicating the key processes and decision points (Figure 1a) and Critical Control Points (Figure 1b) for addressing plant product integrity during the life cycle of biotechnology-derived plants as defined in the five modules of this Guide.

Figure 1b


CONSTRUCT DEVELOPMENT
Construct ID confirmed
No
Disposition
Yes
PLANT TRANSFORMATION
Construct ID confirmed pre-transformation
Host ID confirmed pre-transformation
Material transfer
Transformant ID confirmed
No
Disposition
Yes
CONTAINMENT FACILITIES
Transfer of plant material to containment facility
Transfer of plant material within containment facility
Reproductive isolation within containment facility
Containment of facility
Personnel movement when plants are pollinating
Transfer of plant material from containment facility
Plant product integrity confirmed
No
Disposition
Yes
CONFINED FIELD TRIALS
Material segregation in storage
Material preparation for planting
Transfer of plant material to field
Planting the material
Confinement of field trial
Harvesting the material
Transfer of plant material from field
Plant product integrity confirmed
No
Disposition
Yes
PLANT AND SEED MULTIPLICATION
Material preparation for planting
Transfer of plant material to field
Reproductive isolation
Field activities
Transfer of plant material from field
Storage
Plant product integrity confirmed
No
Disposition
Yes
Transfer and labelling of plant materials (internal operations)
Transfer and labelling of plant materials (external operations)
Order entry and fulfillment
COMMERCIAL PLANT AND SEED DISTRIBUTION

MODULE 1
Research in the Laboratory

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MODULE 1
Research in the Laboratory

The first stages in the development of a biotechnology-derived plant[11] take place in the contained environment of a laboratory and includes activities related to construct development and 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 standard operating procedures.

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

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 usual 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 registerability and societal concerns (e.g., toxicity, allergenicity, antibiotic resistance) should be considered when selecting the coding sequences and gene regulatory elements.

Analyze Product Integrity Concerns

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

[11] 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.

Determine Critical Control Points

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

Establish and Implement:

- Preventive Measures
    - Process for the design of the construct prior to production
    - Verification of the identity and integrity (e.g., sequencing, restriction endonuclease mapping, polymerase chain reaction using construct-specific oligonucleotides, Southern blot with construct-specific probes or other appropriate methods) of the construct
    - Labeling[12], 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 SOPs for traceability
- Monitoring and Verification Procedures
    - Verify the integrity of the construct as designed
    - Confirm identity[13] prior to transfer for plant transformation
- Corrective Measures

[12] For the purposes of this module, 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.

[13] For the purpose of this Guide and unless otherwise indicated, confirmation of identity may be achieved using either procedural confirmation (e.g., documentation) or analytical confirmation (e.g., laboratory assays) or both. This will be determined based on individual circumstances and may warrant a case-by-case assessment.

- In the event that a construct is found to be incorrectly identified or where 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 SOPs as appropriate

- If applicable, train personnel on the procedural changes incorporated

- Record Keeping and Documentation Procedures

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

Plant Transformation and Regeneration[14]

Analyze Product Integrity Concerns

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

[14] The information that follows may also be applied to developing and implementing systems to maintain the identity of plant products derived by techniques other than plant transformation (e.g., RNA interference; cisgenics; genoplasty; targeted genome modification, specifically editing or deleting).

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)

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 SOPs 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, where appropriate
    - During steps to regenerate plant, confirm identity of transformant by documentation or confirm by diagnostic methods, where appropriate
    - Prior to transfer for further propagation, confirm identity of transformant by documentation or confirm by diagnostic methods where appropriate
    - Appropriate 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 SOPs as appropriate
    - If applicable, train personnel on procedural changes incorporated

- Incident Escalation and Response Procedures
    - Documentation to ensure that personnel are trained to support robust systems to report and escalate any incidents of loss of control or containment of GM traits

- Record Keeping and Documentation Procedures
    - Documentation of transformation, regeneration, identity and traceability should be secure, accessible, and retained as appropriate
    - Procedures for the retention of documentation related to non-conformities and follow up actions

Resources for Research in the Laboratory

Regulatory and Other Guidance

It is incumbent on each organization undertaking laboratory research with recombinant organisms to have 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

- FDA/USDA. 2002. Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals. Washington, DC. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124811.pdf

- NIH. 2013. Guidelines for Research Involving Recombinant DNA Molecules. National Institutes of Health, Bethesda. http://oba.od.nih.gov/oba/rac/Guidelines/NIH_Guidelines.pdf

- OGTR. 2013. Guidance Notes for the Containment of Exempt Dealings. Office of the Gene Technology Regulator (OGTR), Woden, ACT. http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/content/ExemptDealGuideJan10-htm http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/content/certifications-1

- WHO. 2004. Laboratory Biosafety Manual. World Health Organization (WHO), Geneva. http://www.who.int/csr/resources/publications/biosafety/Biosafety7.pdf

Inventory Systems for Sample Tracking

Integral to quality management systems that address plant product identity is the implementation of an inventory system to effectively manage identification, labeling, tracking, and disposition of samples (e.g., plasmids, constructs, tissue cultured plants). This is essential to retrieving information pertinent to the identity of a construct or a transformed plant.

There is tremendous variation in how organizations develop their inventory systems to track and control the passage of constructs and biotechnology-derived plants through development and production. Smaller organizations may select a manual or simple automated inventory management system that includes procedures for sample identification—generation of sample labels; generation of replacement labels; tracking changes in status (e.g., sample in storage, sample discontinued); linking sub-samples to source samples; and tracking container-to-container transfers (e.g., for plant tissue culture). Larger or multi-site 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 are collated, sorted, and organized into various report formats based on the type of report required.

At the critical control point of material transfer (e.g., construct to plant transformation, transformant to greenhouse), it is necessary to confirm construct or transformant identity.
Routine inspections of the laboratory may be undertaken to confirm that the appropriate level of containment has been maintained. Inspection activities should be recorded in accordance with an organization's record keeping and documentation procedures.

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@ExcellenceThroughStewardship.org.

MODULE 2

Research in Containment Facilities

DISCLAIMER

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MODULE 2
Research in Containment Facilities

Following plant transformation or another form of targeted genome modification and the regeneration of whole plants *in vitro* (i.e., event[15] 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 to working with biotechnology-derived whole plants[16] 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.

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

- 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
- Misidentification
- Mislabeling
- Errors in tracking
- Errors in disposition

[15] Event refers to 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 transformed with the same or different constructs constitute two events.

[16] This document defines plant as any plant (including plant part) for or capable of propagation. Various references are made to seed and/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.

Determine Critical Control Points

- Transfer of plant material:
    - To the containment facility
    - Within the containment facility
    - From the containment facility for subsequent propagation
- Confirm:
    - Reproductive isolation within the containment facility (where applicable)
    - Containment
    - Personnel movement in and between rooms containing multiple events when plants are pollinating

Establish and Implement

- Preventive Measures
    - Space assignment within the facility
    - Labeling[17], 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 SOPs for traceability
    - Methods and controls for reproductive isolation within the facility (where applicable), for containment, and for effective disposal (e.g., equipment and facility design and maintenance; equipment and facility cleaning)
- Monitoring and Verification Procedures

[17] For the purposes of this module, labeling means to affix with a label (e.g., plant pot tag) that is marked with a name and/or other identifying information (e.g., bar code) that can be used to facilitate confirmation of plant product identity.

- 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[18]

- Monitor facility at regular intervals so that the appropriate level of containment is maintained

- Corrective Measures

  - In the event that plants are found to be incorrectly identified or where identity cannot be confirmed or where reproductive isolation has not been maintained, review the plant material and any derivatives and determine the appropriate disposition

  - Correct any deficiencies identified that could affect integrity of the 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 SOPs

  - If applicable, train personnel on the procedural changes incorporated

- Incident Escalation and Response Procedures

  - Documentation to ensure that personnel are trained to support robust systems to report and escalate any incidents of loss of control or containment of GM traits

- Record Keeping and Documentation Procedures

  - Documentation of analyses, identity and traceability should be secure, accessible and retained, as appropriate
  - Procedures for the retention of documentation related to non-conformities and follow up actions

[18] For the purpose of this Guide and unless otherwise indicated, confirmation of identity may be achieved using either procedural confirmation (e.g., documentation) or analytical confirmation (e.g., laboratory assays) or both. This will be determined based on individual circumstances and may warrant a case-by-case assessment.

Other Stewardship Considerations

Prior to the transfer of *unauthorized*[19] plants from a containment facility to the field, conduct checks of their identity for presence of intended trait(s) and absence of unintended traits (e.g., failure of isolation procedures during pollen flow). Checks can include handling procedures, documentation, or analytical data. To determine an appropriate level of assurance and whether there is a need for additional analytical work, 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 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.

Operating procedures: Experience may provide evidence that plant identity and transgenic purity can be confirmed by use of existing procedures and that additional sampling or a more sensitive analytical method may not be required.

[19] *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.

Resources for Research 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.
  http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/content/ExemptDealGuideJan10-htm
  http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/content/certifications-1

- 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.
  http://www.isb.vt.edu/containment-guide.aspx

Inspection for Containment Facilities

Routine inspection of the containment facility is recommended to confirm that the appropriate level of containment has been maintained. Inspection activities should be recorded in accordance with the organization's record keeping and documentation procedures.

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@ExcellenceThroughStewardship.org.

MODULE 3
Confined Field Trials

DISCLAIMER

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MODULE 3
Confined Field Trials

Within the product life cycle, confined field trials represent the controlled introduction of a biotechnology-derived plant[20] into the environment. As such, their 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 generally are 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 seed in the country of cultivation prior to authorization of the biotechnology-derived plant in key import counties with functioning regulatory systems (see Module 4).

Events may be selected for introgression of the desired trait(s) into elite germplasm. Introgression is 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.

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.

[20] 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.

Analyze Product Integrity Concerns

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

Determine Critical Control Points

- Segregation of *unauthorized*[21] plant material in the country of cultivation
- Preparation of plant material for planting
- Transfer of plant material to the field trial site for planting (includes transfer to intermediate facilities such as field stations prior to planting)
- 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
- Confirmation of confinement
- Isolation to prevent inadvertent cross-contamination during pollen flow
- Storage (if applicable) of harvested material

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

- Use of harvested material in country of cultivation
- Material disposition

Establish and Implement

- Preventive Measures:
    - A procedure for site selection and planning for the controlled environmental release
    - Labeling[22], 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 SOPs for traceability
    - Transfer protocols or processes for traceability across functions, departments, organizations, or locations
    - Protocols and/or SOPs 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 SOPs 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 its leaving the trial site, those for disposition of plant material during season or after harvest, and those for post-harvest land-use restrictions)

[22] For the purposes of this module, labeling means to affix with a label (e.g., on a seed envelope) that is marked with a name and/or other information that can be used to facilitate confirmation of plant product identity.

- Training for individuals involved with activities related to confined field trials

- 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[23]
    - 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 derivatives 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

[23] For the purpose of this Guide and unless otherwise indicated, confirmation of identity may be achieved using either procedural confirmation (e.g., documentation) or analytical confirmation (e.g., laboratory assays) or both. This will be determined based on individual circumstances and may warrant a case-by-case assessment.

- Incident Escalation and Response Procedures
    - Establish and implement an incident response procedure (refer to *Guide for Incident Response Management*)
    - Documentation that personnel are trained to support robust systems to report and escalate any incidents of loss of control or containment of biotechnology-derived plant material
    - 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 non-conformities and follow up actions
    - Processes to communicate changes in regulatory status and trial requirements (if applicable) to relevant parties. For example, the transition of confined field trials from regulated to stewarded status

Resources for Confined Field Trials

Regulatory and Other Guidance

Management of a confined field trial site 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:

- USDA/APHIS Biotechnology Regulatory Services (2012) Permit User's Guide With Special Guidance for ePermits
  http://www.aphis.usda.gov/biotechnology/downloads/permit_guidance.pdf

- USDA/APHIS. USDA-APHIS Biotechnology Regulatory Services (2011). User's Guide: Notification. United States Department of Agriculture, Animal and Plant Health Inspection Service (USDA/APHIS), Riverdale, MD.
  http://www.aphis.usda.gov/biotechnology/downloads/notification_guidance_0311.pdf

- Experimental Use Permits. 40 CFR 172.
  http://www.gpo.gov/fdsys/pkg/CFR-2011-title40-vol24/pdf/CFR-2011-title40-vol24-part172.pdf

- Introduction of Organisms and Products Altered or Produced Through Genetic Engineering Which Are Plant Pests or Which There is Reason to Believe Are Plant Pests. 7 CFR Part 340.
  http://www.aphis.usda.gov/biotechnology/downloads/7_cfr_340.pdf

In addition, the Biotechnology Industry Organization (BIO) has developed two educational tools to assist users in better understanding and meeting the management responsibilities associated with conducting confined field trials in the United States:

- *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.
  http://www.bio.org/articles/plant-biotechnology-containment-analysis-and-critical-control-point-caccp-plan

- *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.
http://www.bio.org/articles/regulatory-guidelines-during-field-trials-biotech-crops

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

- CropLife Canada. Compliance Management Program for Confined Field Trials Course
http://www.croplife.ca/eventscalendar/compliance-management-for-confined-field-trials-course

- CropLife International. (2010). *Compliance Management of Confined Field Trials for Biotech-Derived Plants.* CropLife International, Brussels.
http://www.croplife.org/Files/Upload/Docs/Biotech/FTC%20Manual%20FINAL.pdf

Examples of Forms

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MODULE 4
Plant and Seed Multiplication

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MODULE 4
Plant and Seed Multiplication

Plant[24] 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.

In those countries where seed registration and/or certification are required by law, there are generally four recognized stages of seed multiplication: breeder seed, foundation seed, registered seed, and certified seed[25]. These are also recognized by the OECD Seed Schema as Pre-Basic (breeder seed), Basic (Foundation/Registered seed), and Certified seed. Even in countries that do not require formal registration and certification, the following definitions are generally recognized as the different stages of seed multiplication. Breeder seed is directly controlled by the originating or sponsoring plant-breeding organization. The first increase of breeder seed is usually referred to as foundation seed; it is handled to maintain specific genetic identity and purity. Registered seed is the progeny of breeder or foundation seed and is handled to maintain satisfactory genetic purity and identity. Certified seed is the last stage in the seed multiplication process and is generally produced from foundation or registered seed. Certified seed is the class of seed generally recommended for and used in commercial crop production.

[24] 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.

[25] http://www.aosca.org/Page/Seed_Certification.aspx?nt=96

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.

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[26], and the derived seed or plants need to be handled as *unauthorized*[27] material (see Module 3) or appropriately channeled to avoid trade disruptions.

Analyze Product Integrity Concerns

- Insufficient isolation of plants that does not prevent unintended outcrossing
- Misidentification of plant material to be planted
- Misidentification of plant material harvested and retained
- Inadvertent physical mixture of plant material
- Isolation distances to help address outcrossing and incrossing concerns.
- Errors in disposition
- Incomplete clean-out of planting, harvesting, transporting, and conveying equipment, and storage facilities

Determine Critical Control Points

- Seed packaging, storage, preparation of plant material for planting
- Transfer of plant material to the field for planting
- Disposal of regulated/stewarded treated seed
- Confirmation of reproductive isolation, as necessary

[26] 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.

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

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

Establish and Implement

- Preventive Measures
    - Effective process and procedure descriptions supported by robust training records
    - Quality assurance and control processes to ensure seeds are properly tested, results recorded
    - Labeling[28], 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 SOPs 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

[28] For the purposes of this module, labeling means to affix with a label (e.g., seed bag tag) that is marked with a name and/or other information that can be used to facilitate confirmation of plant product identity.

- Training for individuals involved with activities related to plant and seed multiplication including 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[29] (this applies to plant material that may be used for further multiplication or planting)
    - 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 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 derivatives 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 SOPs as appropriate

- Incident Escalation and Response Procedures
  - Establish and implement appropriate incident response protocol to ensure timely and accurate reporting of corrective actions

[29] For the purpose of this Guide and unless otherwise indicated, confirmation of identity may be achieved using either procedural confirmation (e.g., documentation) or analytical confirmation (e.g., laboratory assays) or both. This will be determined based on individual circumstances and may warrant a case-by-case assessment.

- Documentation to ensure that personnel are trained to support robust systems to report and escalate any incidents of loss of control or containment of biotechnology-derived traits

- Record Keeping and Documentation Procedures
  - Documentation of production, identity and traceability should be secure, accessible, and retained as appropriate
  - Procedures for the retention of documentation related to non-conformities and follow up actions

MODULE 5
Commercial Plant and Seed Distribution

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 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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MODULE 5
Commercial Plant and Seed Distribution

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 a number of 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[30] 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.

[30] This document defines plant as any plant (including plant part) for or capable of propagation. Various references are made to seed and/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.

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

- Errors in product identity
- Errors in trait purity[31]
- Presence of unintended traits
- Inadvertent physical mixture of plant material

Determine Critical Control Points

- Transfer and labeling[32] 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

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

[31] This document defines trait purity as a measure of the extent to which the desired trait is present and unintended traits are absent in a material.

[32] For the purposes of this module, labeling means to affix with a label (e.g., seed bag tag) that is marked with a name and/or other information that can be used to facilitate confirmation of plant product identity.

- 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 SOPs 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[33]

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

- Corrective Measures

  - 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 derivatives

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

  - Incorporate procedural changes into standard operating procedures to prevent recurrence of non-conformities

[33] For the purpose of the *Guide for Maintaining Plant Product Integrity for Biotechnology-Derived Plant Products* and unless otherwise indicated, confirmation of identity may be achieved using either procedural confirmation (e.g., documentation) or analytical confirmation (e.g., laboratory assays) or both. This will be determined based on individual circumstances and may warrant a case-by-case assessment.

- If applicable, train personnel on procedural changes incorporated

- Incident Escalation and Response Procedures
  - Documentation to ensure that personnel are trained to support robust systems to report and escalate any incidents of loss of control or containment of GM traits
  - 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 non-conformities and follow up actions