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Guide for

Product Discontinuation of Biotechnology-Derived Plant Products

DISCLAIMER

The *Guide for Product Discontinuation 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 discontinuing 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 discontinuation process specific to its organization, and (2) in meeting any applicable legal and regulatory 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 Product Discontinuation of Biotechnology-Derived Plant Products provides information on how to develop and implement a stewardship program for Product Discontinuation, wherein sales of the commercial product are terminated. The Guide will assist organizations in designing a program to eliminate product inventories and prevent future market exposure of the discontinued product through the organization's research, development and/or commercial activities.

Purpose

The Guide has been developed as a series of informative educational steps 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 steps is an emphasis on the importance of planning and communication.

Scope

For purposes of this Guide, "discontinued products" are defined as authorized commercialized biotechnology-derived plant products[1] that have reached the end of their commercial life cycle and all sales of materials under the organization's control[2] have been terminated where applicable (see Discontinuation Scope section).

Some steps included may also apply to an organization's project/program discontinuation in the development phase prior to launch due to any reason (for example, project termination during research and development due to budget priorities). For additional information on identification, traceability, and disposition during early phases please see **Modules 1-3 (Laboratory, Containment Facilities, Confined Field Trials)** in the *ETS Guide for Maintaining Plant Product Integrity*.

This situation is separate and distinct from the following out of scope scenarios:

- Product[3] recall and product withdrawal.
- Routine varietal/hybrid succession.

[1] Although this Guide refers to seed product and grain, the guidelines are applicable to other biotechnology-derived plant products. However, this Guide is not intended to address conventional varieties.
[2] Refers to materials and activities under control of the organization (the organization referring to the developer and/ or licensor of the product) conducting the discontinuation and its licensees.
[3] Product and products are used in this guide interchangeably. The discontinuation can include one product or event or multiple products or events.

- Product being sold or taken over by another organization.

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. Accordingly, various entities may be involved in product discontinuation including the developer, licensor, or the licensee. Thus, this Guide refers to the entities that develop traits and/or out-license traits, commercialize traits by self or by others, or in-license traits to commercialize. Paramount to all stewardship programs is communication between these entities with a common goal being the completion of product discontinuation of a biotechnology-derived plant product.

Format of this Guide

This Guide begins with a section dedicated to General Considerations for product discontinuation. Next, the guide explores the three main steps of product discontinuation and expands on the requirements and considerations for each. The Guide is formatted to focus on "product" discontinuation. As noted above, some steps and guidance included may be relevant to an organization's project/program discontinuation.

General Considerations

The decision to discontinue a product is a strategic business decision that should consider many factors, including regulatory requirements, value chain aspects, market dynamics and product replacement. Discontinuation is the final phase of the product life cycle. Discontinuation may be made up of a group of geography-specific discontinuations each with unique timelines that eventually are coordinated to result in global discontinuation of a product.

Discontinuation Scope

The scope of product discontinuation can range from simple and straightforward to complex. Some discontinuations may involve only one product, with limited sales in a single geography, that is not licensed to others, with an allowance for event impurity (Adventitious presence, Low-level presence (AP, LLP))[4]. Alternatively, more complex situations will require a deeper and wider analysis to achieve a complete discontinuation (e.g., multiple products contain the event, product development and sales activities occur within multiple geographies, event and/or products are out-licensed, event or product is present outside of event purity specifications in other products).

Discontinuation Timeline

Generally, an organization will begin to develop a plan for discontinuation once a business decision has been made to discontinue a product. This typically occurs several years prior to the date of last sale. During this period, it is important to develop a strategy for all applicable countries/geographies including identifying the product to be discontinued and establishing the timing of the discontinuation in each geography. The level and length of time that a product may be utilized in the commodity trade value chain can vary depending on the type of crop and market factors. Such variables, and potential implications, should be taken into consideration during establishment and implementation of a discontinuation plan.

[4] As defined in the MPPI Guide, maintaining event purity (i.e. preventing event impurity (AP, LLP)) within the standards determined by an organization, seed association, and/or regulatory governmental authority is critical.

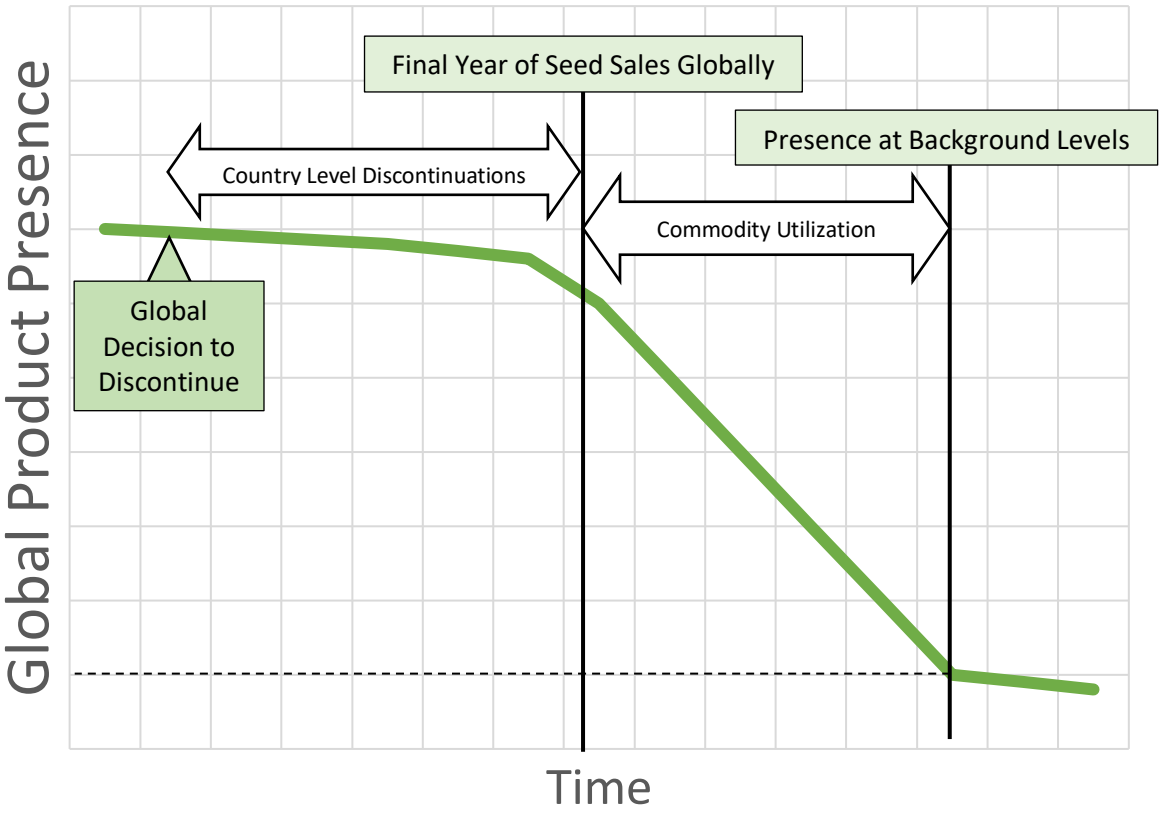
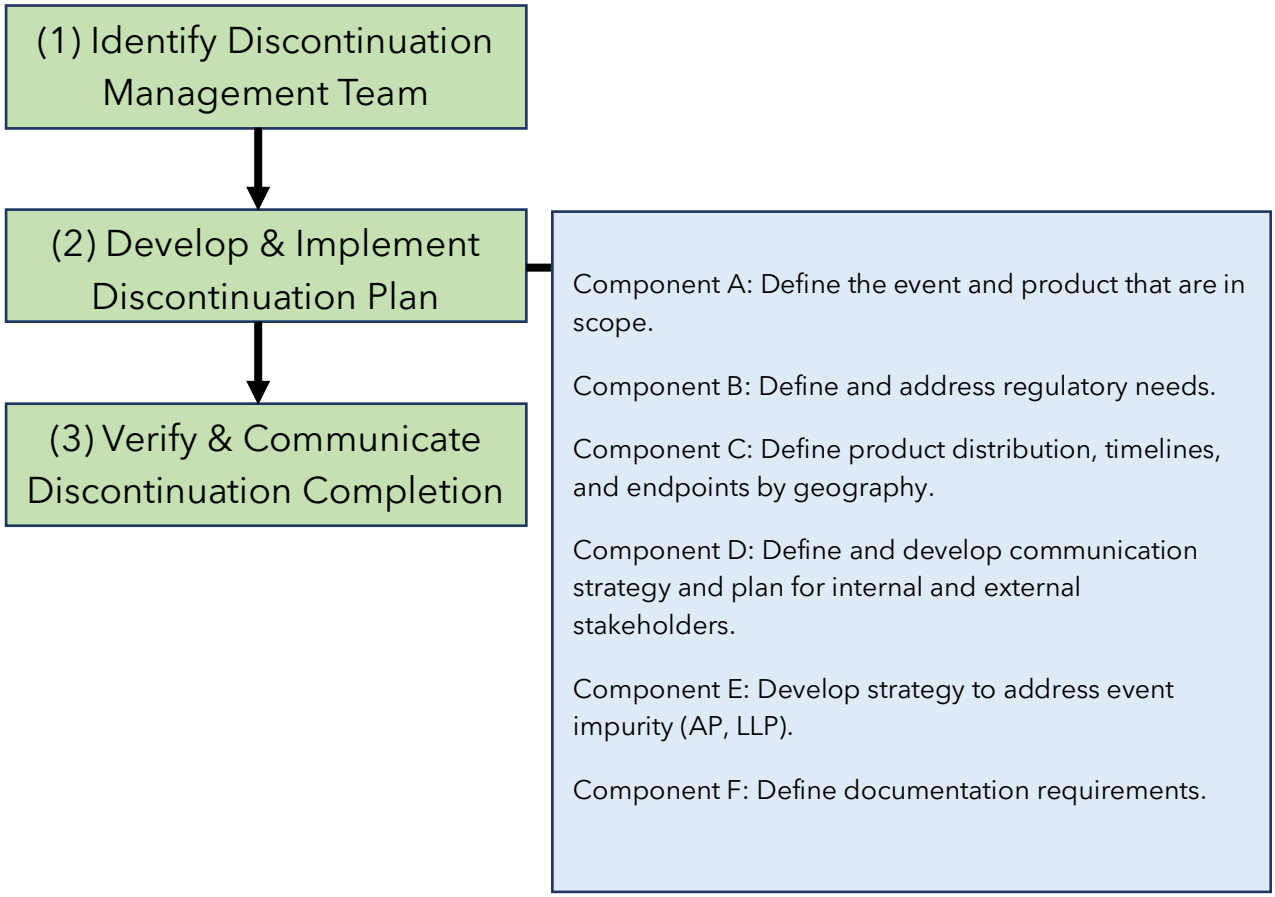


Figure 1: The graphic above depicts an example of the potential dynamics of a discontinuation of a product.

Steps of Product Discontinuation

Once an organizational decision to discontinue a product has been made and the scope, geographies, timing for completion clearly defined, an organization should begin to develop and complete the following three main steps of discontinuation, with the most expansive being step 2.



1) Identify Discontinuation Management Team

Due to the complex nature of a product discontinuation, a multi-disciplinary team, committee, or group is responsible for developing and implementing the discontinuation plan. The discontinuation team responsibilities include all aspects summarized within this Guide and, more broadly, the following:

- Develop, implement, monitor, and update the plan.
- Confirm plan with leadership to ensure alignment on key actions and adequate resourcing.
- Evaluate the impact of potential delays or changes to the plan (e.g., a delay in utilization of seed stock or grain could impact decisions regarding regulatory authorizations and messaging to stakeholders).

- Verify, review, and audit to ensure that the desired endpoints are reached, and the documentation is available to support the activities conducted.
- Once the product discontinuation is complete, the team should remain "on-call" to support any remaining discussions with stakeholders (e.g., regulators, grain trade) and to answer any inquiries or address any reports of potential remaining discontinued product.

Key considerations of the team include:

- Select a leader with appropriate breadth of experience considering discontinuation scope.
- Define representation on the team. This will be determined by the scope and complexity of the discontinuation. Key functional areas to be considered include, but are not limited to, breeding, commercial, communications, legal, licensing, production, quality, regulatory, research, stewardship, supply chain, government affairs and public affairs.
- Verify geographies impacted; define regional or local sub-teams, if needed.

2) Develop & Implement Discontinuation Plan

A discontinuation plan is a key document for the coordination of the discontinuation and includes key actions, deliverables, timelines, and responsibilities. Based on the scope, the discontinuation plan should address geography-specific and function-specific needs, enabling alignment throughout the discontinuation process. The discontinuation plan should be reviewed and updated as appropriate during the discontinuation. Seven key components must be considered in parallel within a discontinuation plan. Thorough description and summarization of each relevant key component will help ensure that the discontinuation plan is adequately mapped out, understood, and executed.

Component A	Define the event and product that are in scope.
Component B	Define and address regulatory needs.
Component C	Define product distribution, timelines, and endpoints by geography.
Component D	Define and develop communication strategy and plan for internal and external stakeholders.
Component E	Develop strategy to address event impurity (AP, LLP).

Component F	Define documentation requirements.

Component A: Define the event and product that are in scope.

Mapping a product's physical location is useful in determining where, within this range, the scope of a discontinuation falls. Factors that could be mapped out to define the scope of discontinuation include:

- Number of commercial products that are being discontinued.
- Specific products that contain one or more events being discontinued.
    - Define any other products, research, or development materials where the event may be present.
    - Define whether the above also are being discontinued.
    - Define by region whether presence of the event being discontinued will be allowed as an event impurity (AP, LLP) in other products following discontinuation.
    - Assess allowances based on each country's applicable regulations.
- Presence of the product (research, development, production, commercial sales, import) being discontinued in multiple geographies as well as with various levels of market penetration.
- Timing of the product discontinuation in each geography due to business needs (e.g., timing may be gradual with product being discontinued in various markets and regions over several years).
- Licensing of product or event to one or more licensees.
- Intellectual Property and legal considerations (e.g., timing of patent expirations).

Component B: Define and address regulatory needs.

Review regulatory status of relevant products[5]

- Evaluate the regulatory status of relevant countries for development, production, and commercialization activities, as well as those impacted in the commodity trade value chain.
- Evaluate each country's regulatory requirements to define the required actions pre- and post-discontinuation. Considerations may include:
    - Some countries require authorization of a stack, whereas other countries require authorization of the individual event.
    - In some countries, authorizations do not automatically expire, so event impurity (AP, LLP) of a discontinued product may remain fully authorized.
    - In other countries, authorizations can automatically expire and may require re-authorization including new data requirements.
- Evaluate what regulatory authorizations need to be maintained post-patent due to organization's commitments (e.g., The AgAccord in the US).

Develop regulatory plan regarding import, food, feed, and cultivation approvals.

- Consider any countries that have time-limited authorizations and facilitate renewals of authorizations as appropriate.
- Consider the nature of the product authorizations and whether other organizations are selling and marketing the product without the initial registrant's approval.
- Consider measures to address any tolerance levels for event impurity (AP, LLP) in seed and grain.

Retain appropriate inventories of materials to serve as reference samples and make available, as appropriate, for verification purposes or stakeholder requests.

Notify government regulators of the formal discontinuation decision and address regulatory requirements, as applicable.

[5] Information regarding the regulatory and commercial status of agricultural biotechnology seed products is available at: biotradestatus.com.

Component C: Define product distribution, timelines, and endpoints by geography.

Identify and describe the following:

- Seed inventory, phase-out, and disposition[6] requirements.
- Existing internal and external seed stocks including development, breeding, and commercial seed.
  - Volume of material stocks
  - Possible areas where seed stocks may be located:

Internal to the organization	Research facilities Greenhouse facilities Breeding locations Testing laboratories Seed archives Seed storage facilities and commercial warehouses Regulatory laboratories/storage facilities Contra-season nurseries Production sites
External to the organization	Academic institutions – breeders, researchers Cooperators Contract Research Organizations Third party archives/repositories for seed/trait Licensees and licensors Distributors and dealers Growers Seed tollers (i.e., Third party producers) Testing facilities Government agencies

Inventory and movement tracking databases necessary for identification and tracking the fate of seed stocks.

Timeline and records for disposition of each type of material including the determination of what should be retained, utilized, or destroyed.

[6] For purposes of this Guide, the term "disposition" is the act or means of settlement of plant material. For example, return to a third party, return to the inventor, or destruction of the material.

- Consider specific Third Parties and Licensees related actions:
    - Identify all affected contracts, licenses, and sub-licenses for development and commercialization activities.
    - Retain records of communication wherein affected third parties and licensees were informed of the intent to discontinue the product.
    - Establish a discontinuation plan with third parties and licensees, appropriate to their situation, including stipulation of any actions, evidence, and documentation required to verify completion of product discontinuation.

Cease Research, Development, Breeding and Production activities.

Inform all research and development, breeding, supply chain, and commercial functions of the decision to discontinue the product and provide the timeline. Include both internal and external groups who may need to modify existing communication materials.

- Modify and/or adapt production plans as needed.
- Document and implement adequate equipment cleanout for equipment used to process/handle the material being discontinued.
- Confirm detection method(s) are available and used in the seed quality management program to confirm, as necessary, absence of discontinued product from ongoing research, breeding, pre-commercial, and/or commercial materials.

Utilize and/or dispose of excess materials and seed stock.

- Determine appropriate means of utilization and/or disposition of excess materials and seed stocks (e.g., lab materials such as DNA, markers, any plant materials etc.). Factors such as local regulatory requirements, commercial considerations, licensing agreements and timing may influence the methods of utilization and/or disposition. Common practice is to utilize materials via normal channels. Where this is not possible because of regulatory, customer, or stakeholder considerations, the appropriate means of destruction should be defined (e.g., autoclave, incineration, landfill). Treated seed may require special considerations.
- Once the appropriate means of utilization and/or disposition is determined, clearly communicate this information along with specific directions to the relevant personnel in a timely manner.

- Sell product inventories according to the defined strategy, where applicable, and track remaining inventory. Record date of last sale.
- Collect and dispose of remaining excess materials and seed stocks according to the defined strategy.
- Archive examples of packaging, then dispose of the remainder of the unused packaging and labels.
- Maintain documentation of disposition and/or destruction, where applicable.

Component D: Define and develop communication strategy and plan for internal and external stakeholders.

Identify key stakeholders, both internal and external

- Including groups such as direct customers, licensees, commercial partners, regulatory agencies, and downstream stakeholders (including the food and feed industry) and determine levels of communication required during the discontinuation process.

Provide appropriate information regarding the discontinuation plan, geographies, and timelines to help achieve discontinuation.

- Include a reminder that discontinuation is the final phase of the product life cycle.

Engage stakeholders according to their needs and concerns through dialogue and updates.

- Use appropriate communication tools, such as: computer databases, telephone, email, net meeting, webinar, websites, trade press and media releases.

Communicate:

- The product replacement plan, if applicable.
- Deregistration of varieties and hybrids, if applicable.

Component E: Develop strategy to address event impurity (AP, LLP).

Country-specific requirements.

Define country-specific allowances and update specifications to address the presence of product/event as event impurity (AP, LLP).

- Establish quality management practices.
- Implement changes that may be relevant to quality management systems, including modification of testing specifications and critical control points.

Across the research, development, breeding, and commercialization processes.

- Verify critical control points are defined, established, and that responsibilities for quality management are assigned.
- Establish appropriate thresholds and quality control procedures that will detect the discontinued event with appropriate specificity, sensitivity, and reliability during an appropriate length of time.
    - Define appropriate test methods for verification purposes to be used during the discontinuation process.
    - Monitor output from this quality control system.
    - Follow up on any unexpected findings with remedial actions to:
        - Identify and contain materials as needed.
        - Appropriately dispose of materials.
        - Identify source(s) and implement measures to minimize reoccurrence.

Component F: Define documentation requirements.

Recordkeeping is an important part of a product discontinuation. It is important to identify what records must be retained, such as material disposition or testing results, and to define record retention requirements.

Example records that may need to be maintained	Records related to inventory depletion, date of last sale, and disposal & material fate. Internal and external databases/website listings. Third-party agreements and termination documentation. Detection methods. Stewardship-relevant documents (e.g., instructions, decision records, quality control records). Regulatory documents. Documents supporting internal verification process and audit records. Discontinuation Team documents (e.g., membership, key decisions, Discontinuation Plan, summary report). Inventory of retained material.

3) Verify & Communicate Discontinuation Completion

- The completion of the product discontinuation needs to be verified according to the verification strategy defined within the discontinuation plan including, for example:
    - A review of the discontinuation plan and verification that important actions have been completed and documented (e.g., documentation of utilization and/or disposition of seed stock).
    - A verification that planned audits have been completed and findings have been addressed. A final audit of facilities, records and other relevant materials may be completed.
- When all materials have been appropriately disposed of, completion of the product discontinuation needs to be communicated to relevant stakeholders:
    - Prepare summary report of product discontinuation, including date(s) of last sale and key activities completed.

- Communicate completion of product discontinuation to both internal and external stakeholders according to the communication plan. For example:
    - Update of external databases/website listings.
    - Identify on-call team members to address subsequent questions or potential issues.

- Archive the records related to the product discontinuation.
- Develop the strategy to verify completion of the production discontinuation.

The verification strategy should address both the organization and licensees or other partners. The strategy may include management system reviews, audits of records, site inspections, or use of third-party inspectors, to verify the product has been discontinued.

Guide Summary

Within this ETS Guide for Product Discontinuation of Biotechnology-Derived Plant Products, the following are described: general considerations for product discontinuation, the three main steps of product discontinuation, and further guidance for each step. In addition, explanations of how the discontinuation process should be adapted to the specifics of the organization and the product involved are provided to assist each respective organization in customizing their specific approach for product discontinuation.

The intended outcome of addressing this guidance, is a robust coordinated industry approach to regional and/or global commercial biotechnology-derived plant product discontinuation.

Abbreviations/Acronyms

AP	Adventitious presence
DNA	Deoxyribonucleic acid
ETS	Excellence Through Stewardship
LLP	Low-level presence
QMS	Quality Management System

Definitions

Please refer to the ETS Guide for Maintaining Plant Product Integrity