**BIOTECHNOLOGY INDUSTRY ORGANIZATION**

# Reference Document for

# Confinement and Development of Plant-Made Pharmaceuticals

# in the United States

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# Biotechnology Industry Organization

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## Executive Summary

The term "plant-made pharmaceuticals" is used to describe a new category of transgenic plant-based products that offer the potential to use renewable resources to create new types of life saving drugs to prevent, treat and cure major diseases that afflict hundreds of thousands of people. Using the techniques of modern biotechnology, pharmaceuticals can be produced efficiently from relatively small acreages using domesticated crops by combining elements of traditional pharmaceutical manufacturing and well-established crop production practices.

The Biotechnology Industry Organization (BIO) and its member companies involved in the development and commercialization of plant-made pharmaceuticals are committed to ensuring the safety of these products during all stages of development and production. This means a commitment to full compliance with all applicable laws, regulations and guidance – the regulatory framework – from regulatory agencies that oversee the development and production of plant-made pharmaceuticals. Federal regulatory agencies provide the regulatory framework for all transgenic plants. This framework is currently applied to plant-made pharmaceuticals and rigorously followed by the industry.

A critical part of the application of the regulatory framework to plant-made pharmaceuticals focuses on the development and implementation, on a case-by-case basis, of measures to control exposure to the transgenic plants and their expression product(s). Exposure control will be achieved through confinement systems and procedures designed to:

- prevent inadvertent human exposure through food and feed, and
- minimize occupational and environmental exposure.

Today, the industry is conducting research in small-scale plots. With significant large-scale production on the horizon, the opportunity exists to further enhance our understanding of the government's requirements and to develop best practices and procedures to ensure proper application and stringent compliance.

<u>Key Regulatory Assumptions</u>

Existing statutes and regulations are appropriate for oversight of the production of plant-made pharmaceuticals, and standardized approaches to risk assessments currently exist and are effectively used by regulators. This will continue to be the case as the production of plant-made pharmaceuticals expands from small trials to larger ones and eventually to commercial production.

Current regulations allow for the production of transgenic crops only after a comprehensive risk assessment has been completed and conditions tailored to the particular crop and expression product(s) have been applied. Because of the unique characteristics of pharmaceutical-producing crops, BIO supports the regulatory determination that these crops will always be grown under confinement and produced in a regulated environment. As part of that regulatory process, BIO recommends that the appropriate government agencies oversee the application of science-based confinement procedures, including on-site inspections. Industry is committed to fully cooperating with the agencies in these reviews and inspections, and to supplying the agencies with the validated analytical methods for detection and compliance.

Key Plant-Made Pharmaceutical Development Practices

In order to ensure that the production of plant-made pharmaceuticals complies with all regulatory requirements, the industry must continue to adhere to a rigorous set of crop production and handling practices. Seeds for plant-made pharmaceuticals will not be sold through conventional channels, but will only be made available to pre-qualified contract growers. Processing, milling and extraction will be conducted outside commercial food and feed channels to prevent co-mingling.

Each company will be responsible for developing confinement procedures, specific for their crop and product, which are consistent with regulatory guidance and the recommendations of this document. These confinement procedures will become Standard Operating Procedures (SOPs) for the company. Key elements of SOPs for a confinement system include:

- training
- contracts and channeling
- site selection and security
- crop production
- identification
- containers
- equipment
- disposition of plant material
- verification
- compliance assessment
- monitoring
- remediation

The SOPs for confinement will be stringently applied to prevent inadvertent human exposure through food and feed. Adherence to these same SOPs will also prevent or limit exposure to the expression product or to plant material containing the expression product to ensure safety to humans and the environment during production. Consistent with current regulations, SOPs should be reviewed by regulatory authorities to determine that they are sufficient to ensure that the appropriate level of confinement is maintained. Furthermore, company SOPs for confinement should become an integral part of the APHIS permitting and approval process. In addition, the industry will fully cooperate with regulatory agencies in overseeing the design and

application of science-based confinement procedures, and will provide the agencies with validated analytical detection methods to facilitate this activity.

Each pharmaceutical crop will be produced, handled and marketed within an Identity Preservation (IdP) system that will keep the crop segregated from other crops and establish specific protocols for the production and handling of the crop. IdP systems are designed to prevent contamination of the plant-made pharmaceutical. An integral element of an IdP system is the adoption of "chain of custody" procedures to ensure control of the product by the developing company during all stages of production. Rigorous adherence to the confinement procedures adopted for each crop will be a key factor in meeting the objectives of the IdP system. Because of this reliance on confinement, IdP systems complement the control of exposure that confinement procedures are designed to achieve.

Implementation of the practices and procedures set forth in this document will allow industry to deliver on the promise of plant-made pharmaceuticals in a manner that ensures the minimization of any potential risks to consumers, workers or the environment that might be associated with the production of these products.

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## I. Introduction

Plant-made pharmaceuticals are the result of an innovative application of biotechnology, whereby plants are genetically modified to produce new drugs and biologics that can prevent or treat diseases and save lives. The use of transgenic plants to produce pharmaceuticals will enable the commercialization of life-saving products that may otherwise not be available to the patients who need them. This technology will allow the production of drugs and biologics at a scale and cost that might not be possible with other systems. Beyond cost and scale, plant-made pharmaceuticals will be produced by a process that is fully sustainable because the plants and crops used as raw materials are renewable resources.

Few, if any, manufacturing processes are risk free, nor do health, safety or environmental laws require zero risk. To minimize the risks associated with the production of plant-made pharmaceuticals, the regulatory framework and industry best practices should focus on the development and implementation, on a case-by-case basis, of measures to control exposure to the transgenic plants and their expression products. Exposure control will be achieved through confinement systems and procedures designed to prevent inadvertent human exposure through food and feed and to minimize occupational and environmental exposure. Confinement includes all measures necessary and appropriate to control access and exposure to the transgenic plants and their expression products, including environmental exposure and access and exposure to humans and other animals.

The Biotechnology Industry Organization (BIO) believes in the promise this technology holds to treat and cure major diseases that afflict hundreds of thousands of people – such as heart disease, allergies, cancer, diabetes, Alzheimer's and others. Our members as an industry are committed to taking all necessary measures to protect human health and the environment. We are working closely with government regulators to ensure that current and future health, safety and environmental regulations and industry practices are both rigorous and enforceable.

In that context, this document (1) represents our understanding of how plant-made pharmaceuticals are treated within the existing regulatory framework; (2) recognizes that the designated regulatory officials are ultimately responsible for the mandatory processes and decisions affecting the regulatory status and production of these products; (3) recommends procedures for confinement and exposure assessments consistent with this framework that consider the unique characteristics of plant-made pharmaceuticals; and (4) states our continued commitment to the procedures required to ensure compliance and good product stewardship. Companies involved in the development and commercialization of these products will undertake responsible stewardship to ensure the safety of food, feed, workers and the environment and are committed to meeting that responsibility.

While this document and recommendations focus on plant-made pharmaceutical products, it is anticipated that the principles and recommended practices and procedures will generally be applied to other non-food use products produced in plants.

## II. Regulatory Background

Food and feed crops bioengineered to be resistant to insects and disease or tolerant to specific herbicides have been in commercial production for nearly seven years. The development and commercialization of these products has been regulated by the United States Department of Agriculture (USDA), the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA). These agencies also regulate plant-made pharmaceuticals under the same regulatory framework. The basic outline of this regulatory framework follows.

USDA's Animal and Plant Health Inspection Service (APHIS) regulates biotechnology-derived crops under the authority of the Plant Protection Act, 7 U.S.C. 7701-7758, which authorizes the agency to prohibit the movement of plants or plant products considered "plant pests" or "noxious weeds." The agency's definition of plant pest includes parasitic plants or similar organisms that can directly or indirectly injure or damage plants, while a noxious weed is broadly defined as any plant or plant product that can directly or indirectly cause damage to agriculture, human health, or the environment. APHIS has issued regulations regarding the introduction of biotechnology-derived plants. 7 C.F.R. Part 340.

Until APHIS makes a science-based determination that a biotechnology-derived plant does not warrant further regulation, the plant is considered a "regulated article" and cannot be introduced into the environment without first either obtaining a permit or submitting a notification. APHIS has provided guidance to the developers of all transgenic plants to control the movement of expression products and plant material containing the expression product during development. Typically, crops cleared for commercial introduction no longer require the confinement measures that were required by APHIS at the field test stage. In contrast, APHIS considers all pharmaceutical-producing plants to be "regulated articles" regardless of the stage development. As such, these plants are not eligible for field testing by notification and may not be introduced into the environment at any time without a permit from APHIS. BIO strongly endorses the decision by APHIS to continue its regulatory oversight of these plants through commercialization and impose carefully tailored, science-based confinement procedures by permit during commercial production.

In making a decision on a permit for these crops, APHIS must conduct an analysis of the environmental effects of this decision under the National Environmental Policy Act (NEPA), 42 U.S.C. 4321 *et seq*. NEPA requires every government agency to assess the consequences of its proposed actions on the environment prior to making an environmentally significant decision and to make that assessment available to the public. A NEPA analysis will typically also address any other environmentally-related potential issues the agency action may raise under federal laws such as the Endangered Species Act or the Federal Migratory Bird Treaty Act.

The FDA has overall responsibility for the safety of the food supply and reviews the safety and nutritional aspects of all biotechnology-derived crops intended for food or feed under the

authority of the Federal Food, Drug, and Cosmetic Act (FFDCA). FDA bases its clearance of these crops on a review of any quantifiable changes in the plant caused by the addition of the transgene, a characterization of the added genetic information, an assessment of the safety of the expression products and other similar factors set forth in its 1992 Statement of Policy: Foods Derived From New Plant Varieties. FDA has recently proposed a rule that would make this review process mandatory.

In addition to all other regulatory clearances, insect-resistant and disease-resistant crops require approval by EPA. In the U.S., the expression product (i.e., protein) in an insect- or disease-resistant crop must be cleared by the EPA as a pesticide under section 3 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 U.S.C. 136a, for various human health and environmental concerns, and under section 408 of the FFDCA, 21 U.S.C. 346a, for food safety purposes. EPA has issued regulations for these pesticidal expression products, which it refers to as "plant-incorporated protectants." 40 C.F.R. Part 174. In appropriate instances, EPA has imposed various confinement-related requirements on these crops during field tests, in commercial production, or both.

The evaluation, production and distribution of the final products derived from pharmaceutical-producing plants will be regulated under existing regulatory requirements administered by FDA or USDA depending on the nature of the products and their intended use. Plant-derived biologics and drugs, intended for diagnostic, preventive or therapeutic use in humans are regulated by the FDA under authority of the Public Health Service Act , 42 U.S.C. 201 *et seq.,* and the FFDCA, 21 U.S.C. 301 *et seq.,* respectively. USDA's Center for Veterinary Biologics regulates biologics for use in animals under the authority of the Virus-Serum-Toxin Act (VSTA), 21 U.S.C. 151-159. FDA's Center for Veterinary Medicine regulates drugs for use in animals under the authority of the FFDCA. In addition to the assessment of potential environmental impacts by APHIS, NEPA would also require FDA or USDA, as appropriate, to consider any additional environmental impacts that might be associated with the licensing of plant-made pharmaceuticals as part of the drug or biologics licensing process.

The Occupational Safety and Health Administration (OSHA) regulates workplace safety, including the safety of those working with plant-made pharmaceuticals. OSHA requires employers to maintain a workplace "free from recognized hazards." Manufacturers must evaluate the substances they produce to determine whether they may pose physical or health hazards to exposed employees.

The regulatory process for a plant-made pharmaceutical will differ in certain respects from the process that has been employed to date for non-pharmaceutical products. The human and environmental risk assessments conducted for plant-made pharmaceuticals will, however, be guided by many of the same, science-based policies and procedures that have been used to date by APHIS, FDA and EPA for non-pharmaceutical producing crops.

## III. Pharmaceutical-Producing Crops

Crops that have been identified as good potential sources for production of pharmaceuticals include alfalfa, canola, corn, potato, rice, safflower, soybeans and tobacco. These crops offer

significant practical advantages. They are very efficient factories for pharmaceutical products and can be grown cost-effectively using current agricultural methods. In addition, an extensive knowledge and experience base exists for the efficient production and precise handling of these crops.

While tobacco has the necessary characteristics for production of pharmaceutical products, few other non-food crops that are domesticated have the necessary characteristics for the expression of pharmaceutical products. As a result, the majority of plant-made pharmaceuticals are currently and, for the foreseeable future, will continue to be produced in crops that are also used as food and feed. These crops offer numerous safety and regulatory benefits, including the following:

- The crops are well-characterized with respect to pollination, seed dormancy, tendency to weediness and other factors necessary to develop confinement procedures.
- The crops usually do not produce toxins or anti-nutritionals.
- Any contaminants present in the crops are well-characterized.
- The crops may be less likely to be invasive of unmanaged ecosystems.
- The harvested commodities may allow for oral delivery of pharmaceuticals that are orally active.

## IV. Principles for Control of Exposure to Plant-Made Pharmaceuticals

Preventing Inadvertent Human Exposure through Food or Feed

Industry must develop and implement confinement systems and procedures that are designed to prevent inadvertent human exposure through food and feed to the transgenic plants and their expression products. Such confinement procedures will be tailored to the particular crop and expression product being tested or produced and to the size, location and other characteristics of the test plots or production acreage involved. Confinement procedures will be reviewed and approved by regulatory authorities prior to approval of field trials or production, and sites will be inspected to ensure that confinement objectives are being met.

Minimizing Direct Exposure to Humans and the Environment During Production

Industry must develop and implement confinement procedures that are designed to minimize occupational and environmental exposure to the transgenic plants and their expression products. An examination of any potential risks to humans and the environment during the production of plant-made pharmaceuticals must be based on an analysis of both the potential toxicity of the expression product and potential exposure routes. Confinement procedures, discussed below, are applied during the production stage to prevent or limit exposure as required by a plant-specific risk assessment. This may result in very stringent confinement procedures during the early development stages to prevent or reduce human and environmental exposure, with a concomitant reassessment of confinement procedures as data become available on which to better quantify the risks, assuming the data support such a reduction.

Principles of Confinement

BIO and its member companies involved in the development and commercialization of plant-made pharmaceuticals support the conclusion that controlling exposure to plant-made pharmaceuticals can be best achieved through the application of appropriate confinement systems and procedures at all levels of production. Confinement includes all measures necessary and appropriate to control access and exposure to the transgenic plants and their expression products, including environmental exposure and access and exposure to humans and other animals.

The industry's approach to confinement and the recommended confinement systems and procedures are based on the following principles:

- Confinement must be designed to prevent inadvertent human exposure to plant-made pharmaceuticals through food and feed.
- Confinement must be designed to minimize occupational and environmental exposure to plant-made pharmaceuticals during all phases of production.
- Companies developing these products will (a) ensure rigorous compliance with confinement measures, (b) share with appropriate regulatory agencies validated analytical methods or testing for the detection of the relevant expression products, and (c) fully cooperate in reviews of confinement measures and on-site inspections by appropriate government regulatory agencies.
- Confinement systems and procedures must be based on sound scientific principles

Each company must develop specific procedures that are appropriate for the product under development and the crop system being utilized to produce that product. These procedures should be consistent with existing, relevant regulatory guidance and the recommendations included here.

## V. Agency Review and Approval of Confinement Procedures

The current APHIS regulations governing all transgenic plants require confinement as the basis for controlling the movement of the regulated articles. These confinement measures have been effectively applied to field trials and small-scale production of plant-made pharmaceuticals, and will also be used in the large-scale production of these products.

All field-testing of pharmaceutical-producing plants requires approval from APHIS prior to planting. The industry anticipates and supports the agency's expressed position that this procedure will continue and that commercial production of these products will be regulated in a similar manner for the foreseeable future. The industry recommends that the specific procedures for ensuring confinement, as discussed in the next section, be reviewed by APHIS on a case-by-case basis as part of the permitting process. Procedures for the prevention of co-mingling and outcrossing should be reviewed at the time of the initial permit for the specific product. Some procedures may be crop specific and will not change from product to product within the same crop. Other procedures, such as those relating to environmental or direct human exposure, will be product specific but may change as additional data become available. Modifications to these

procedures should be submitted for review and concurrence on an as-needed basis. These procedures may have to be reviewed and approved with each new permit to take into consideration increases in acreage and new safety data that have become available.

Beyond approving trials and production of pharmaceutical producing plants in advance, the industry also recommends that the appropriate regulatory agencies review confinement procedures in the field, including on-site inspections, to ensure that confinement objectives are attained. Industry is committed to fully cooperating with the agencies in these reviews and inspections, and to supplying the agencies with the validated analytical tools required for detection and compliance.

## VI. Plant-Made Pharmaceutical Development Practices

The adventitious presence of an expression product in food and feed may result from (1) the unintended co-mingling of pharmaceutical-expressing plant material with plant material intended as food or feed, and (2) the lateral movement of genes via seed dispersal or pollen flow from a pharmaceutical-expressing plant to another related species intended as food or feed. Seed dispersal and pollen flow may also result in unintended environmental exposures.

To control these potential sources of exposure and to minimize occupational and environmental exposure to plant-made pharmaceuticals during all phases of production, it will be necessary to develop and implement production practices that are defined by stringent, written Good Agronomic Practices and Standard Operating Procedures (SOPs) rigorously applied from field preparation through post-harvest monitoring of fields that have been used for the cultivation of the product. It will also be necessary to follow stringent procedures for the handling and movement of plant material containing the expression product.

Identity Preservation (IdP) systems are designed to maintain product integrity and prevent contamination of the plant-made pharmaceutical. An integral element of an IdP system is the adoption of chain of custody procedures to ensure control of the product by the developing company during all stages of production. Rigorous adherence to the confinement procedures adopted for each crop will be a key factor in meeting the objectives of the IdP system. Because of this reliance on confinement, IdP systems complement the control of exposure that confinement procedures are designed to achieve.

### Confinement Systems to Control Exposure

The industry will control exposure to plant-made pharmaceuticals through confinement procedures applied to agronomic and crop handling practices specific to the crop, expression biology and geography of the area where production is intended to occur.

The control of exposure can be achieved by a system of SOPs that consider every aspect of crop production and handling. This system includes the training of all individuals involved with production. SOPs also include a process of sign-offs and inspections to ensure all procedures have been followed. The final element of the SOPs is a validated scientific method for detection of the plant-made pharmaceutical that will be provided to the appropriate government regulatory

agencies.

SOPs are made for each element of a confinement system. Since each crop and production area represents a different situation, these recommendations are presented as general guidance with the expectation that each company will work with all production groups to arrive at SOPs consistent with these recommendations and the appropriate regulatory guidance. The SOPs will be made available to regulators and reviewed as part of the permitting and approval processes.

The elements of SOPs for a confinement system include:

- **Training**
  The training of growers and all other individuals involved with the development and production of plant-made pharmaceuticals is essential to the effectiveness of a confinement system. While elements of the training are specific to the prevention of co-mingling, the training program must consider and address the potential for occupational and environmental exposure.

- **Contracts and channeling**
  Seed for plant-made pharmaceuticals will not be sold through conventional channels. These seeds will only be made available to pre-qualified contract growers. Processing, milling and extraction will be conducted outside commercial food and feed channels to prevent co-mingling.

- **Site selection and security**
  Field-testing and production sites must be selected and secured in order to obtain the appropriate confinement levels. This may require, among other options, considerations of inadvertent co-mingling with similar transgenic or non-transgenic crops in the near vicinity if there is a risk of plant material being accidentally moved to an adjacent field. Site selection must be considered from the point of confinement of plant material to the specific production site and minimization of exposure to the environment and non-target organisms. As necessary, security measures must be designed to provide an appropriate degree of control over access and exposure to the site and crop, including by birds, other animals and human intruders.

- **Crop production procedures**
  All procedures associated with the production of a specific crop represent areas where exposure can potentially occur. The procedures associated with seed production, planting, growing, harvesting, transportation and storage are generally consistent across different crops, but each crop has elements that are unique to that crop. All procedures must be examined as a method of identifying where exposure can occur. As necessary, these procedures should be modified and confinement procedures written specifically for that activity or element and incorporated in the relevant permit. A variety of physical, biological and temporal confinement procedures may be employed as necessary to prevent exposure through food and feed or to limit environmental exposure to a specific crop or expression product. Such confinement procedures might include border rows, isolation distances, temporal separation, sentinel plots and male sterility technology. Where

warranted based on an assessment of the specific protein, crop and expression biology (e.g., at what level do different plant materials contain the expression product), procedures to minimize occupational exposure must be implemented. Typical procedures to prevent or limit direct human exposure as determined by the expression product and expression profile within the plant are the use of protective clothing, breathing devices, limitations on entry, and cleanup procedures after crop contact.

- **Identification**

Plant-made pharmaceutical crops and plant material derived from the crop must be distinguishable to the developer through clear identification methods (e.g., labeling) during all production phases. This will involve identification of seed, fields, grain, storage units, transportation equipment, planting and harvesting equipment and elements and items related to production. The identification method must be unique enough that the transgenic crop is always clearly distinguishable from any other crop.

- **Containers**

Containers and packing materials to be used for shipment, transportation or storage must be selected on the basis of integrity, location (if appropriate) and ability to be thoroughly cleaned or disposed of, and must be properly labeled at all times.

- **Equipment used in production, storage and processing**

Any equipment used to process planting seed, transport seed and grain, plant seed, harvest seed or grain, store seed and grain and initially process the plant material containing the desired expression product must be dedicated to the specific product or thoroughly cleaned prior to use with any other crops, including crops intended as food or feed. Such change over cleaning procedures must be validated. The decision as to which procedure to use should be at the discretion of the developer.

- **Disposition of plant material**

All unused plant material, both on farm and off, must be disposed of in accordance with applicable regulatory guidance and in a manner that will prevent inadvertent exposure, including co-mingling with plant material intended as food or feed.

- **Verification**

Verification should be achieved through a system of documentation and record-keeping, including checklists and sign-offs at those stages of production considered essential to achieving confinement. These may be different for each crop and will be incorporated into the system.

- **Assessment of compliance**

Central to this system are assessment procedures performed at appropriate points to ensure that the system and verification procedures are functioning as intended. These assessment procedures may include internal as well as external reviews and inspections, as appropriate.

- **Monitoring of production sites**

The monitoring of field trial and production sites for crop volunteers is required by existing regulations and guidance for an appropriate period after harvest of the transgenic crop. Any unusual occurrence, including deleterious effects on plants, non-target organisms or the environment, must be reported to the appropriate regulatory agency. Field trial and production sites must also be monitored during growing and after harvest to ensure that all plant material remains at the specific site until disposed of in accordance with designated procedures.

- **Remediation**

Contingency plans must be developed and appropriate remedial measures employed in the event monitoring confirms that confinement has not achieved the desired result. In addition to immediate mitigation measures, it may be necessary to modify and/or intensify appropriate elements of the confinement system in order to improve future performance. Where circumstances warrant, future planting may be suspended until the necessary modifications to the confinement system have been instituted.

Control of Cross Pollination

Unintended human or environmental exposure resulting from cross-pollination with a pharmaceutical-producing plant of the same species represents the most discussed and debated route through which unintentional exposure may result. Regulatory agencies provide guidance and procedures for achieving physical, biological and temporal isolation to control cross-pollination. The basic elements of the recommendations made here are consistent with this existing guidance. The areas that should be considered when developing specific procedures to control cross-pollination are:

- The crop – The reproductive characteristics of the specific crop must be considered when selecting and implementing specific confinement procedures.

- Expression product characteristics – Where in the plant is the pharmaceutical expressed and when is it expressed? An expression product produced only in leaves in a crop that is harvested prior to pollen development will have different considerations than an expression product produced in seed or grain.

- Pollen characteristics – The primary considerations here are the pollen viability, dispersion mechanism, effective dispersion distance, and characteristics of the crop.

- Geography – The specific area where the biological or pharmaceutical-expressing plant is grown and the resulting proximity to crops of the same or related species are considerations in implementing confinement procedures.

- Time – Temporal separation of flowering for the pharmaceutical-producing plant from nearby crops of the same or related species.

Confirmation of Confinement

A key element of oversight of confinement practices by regulatory agencies would be the implementation of testing to ensure that confinement measures are achieving the desired result. This will require the use of validated analytical techniques and appropriate sampling methodologies in order to provide a high level of confidence (> 95%) in the test results. Such a testing scheme would comprise sampling seed, grain or plant material to obtain a sample representative of the lot to be tested.

The presence of transgenic DNA from a pharmaceutical-producing plant in a particular agricultural commodity should serve as an indicator that 100% confinement has not been achieved. However, such a finding is not considered proof that the expression product associated with that DNA is present. Rather, the presence of the DNA will trigger further examination of the commodity for the presence of the specific expression product associated with the DNA using scientifically validated methods of analysis supplied by the plant's developer.

Individual companies will make available to regulatory agencies validated analytical methods for the detection of each expression product in the specific crop used for production. These analytical methods will be the best available methods for detection. Should the transgene associated with a specific expression product be found in an agricultural commodity, the regulator would analyze that commodity for the presence of the expression product using the analytical method provided by the responsible company or a modified method as appropriate for the specific commodity. Companies will 1) conduct their own analyses of agricultural commodities to confirm confinement and 2) fully cooperate with regulatory agencies in their crop analyses and their reviews and on-site inspections of companies' confinement procedures.

Identity Preservation Systems

As stated earlier, pharmaceutical crops will be grown, handled and processed under Identity Preservation (IdP) systems, both at field trial and commercial levels of production. A rigorous IdP system will assure that the identity and purity of the crop is maintained throughout, including planting, harvesting, transportation, storage, processing and production. This will significantly enhance the developer's ability to deliver a plant-made pharmaceutical that conforms to legal and regulatory requirements and meets contractual specifications.

Each company will establish an IdP system that ensures pharmaceutical crops will be completely segregated from other crops, both similar and dissimilar. An integral element of an IdP system is the adoption of "chain of custody" procedures to ensure control of the product by the developing company during all stages of production. In addition, detailed production and handling procedures will be established including specific operating procedures for confinement. Rigorous adherence to the confinement procedures adopted for each crop will be a key factor in meeting the objectives of the IdP system.

The application of chain-of-custody procedures to an IdP system ensures thoroughness and accuracy. These procedures are primarily observations and sign-offs at points in the production

process before and after an activity that involves handling of the product. For example, a form may be utilized on which a responsible individual confirms by his or her signature that a specifically harvested crop was loaded from the harvester to a designated vehicle for movement to a designated storage facility. A responsible individual at the storage facility then signs the same form indicating that the transportation vehicle, and therefore the crop, arriving at and unloaded into the storage facility is the same as that loaded at the field. These or similar procedures applied to all stages where a product is handled will ensure and document a chain-of-custody for the product.

## VII. Conclusion

Plant-made pharmaceuticals offer great promise to prevent, treat and cure major diseases that affect hundreds of thousands of people. Industry is committed to protect human health and the environment in the production of these life-saving treatments. This means a commitment to regulations and guidance from government agencies that oversee the production of these plant-made pharmaceutical products and the development and implementation of industry practices to assure compliance. This document has provided our understanding of the relevant regulatory process and stated the industry practices that will be used to comply with that process. It is our firm belief that the benefits of plant-made pharmaceuticals outweigh the risks incurred in their production and that guidance issued under the existing regulatory framework, together with industry practices outlined in this document, will ensure that that concomitant risk is minimal.