EXCELLENCE THROUGH STEWARDSHIP®

Advancing Best Practices in Agricultural Biotechnology

Guide for Resistance Management

for Biotechnology-Derived Plant Products

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The *Guide for Resistance Management for 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 resistance management 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.

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October 2014

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Introduction

Integrated Pest Management (IPM) is a holistic approach to sustainable agriculture that focuses on managing pests (e.g., weeds, insects) using a combination of sound agronomic best management practices (i.e., cultural, biological, and chemical methods) that minimizes pest damage and maximizes the availability and longevity of tools needed for pest management (for a detailed IPM definition, see the Definitions section). IPM includes the responsible use of crop protection and plant biotechnology products including developing, implementing, and promoting resistance management plans. Resistance management is important to support the increasing global demand for food. Growers must be able to maximize production sustainably while minimizing losses and protecting biodiversity and the environment. Key components to be considered in integrated pest management and resistance management strategies include:

- Preventing the build-up of pests
- Preserving natural enemies within the cropping system (e.g., insect predators)
- Monitoring crops for pests and natural control mechanisms
- Intervening when additional control measures are needed
- Using multiple complementary control tactics

Purpose

This Guide assists developers of biotechnology-derived plant products by providing guidance on the development and implementation of a resistance management program(s) that includes a resistance management plan(s) as components of an IPM strategy throughout the product life cycle from research and discovery through commercialization and post-market activities[1].

Scope

This Guide addresses items to consider in developing and commercializing biotechnology-derived plant products including assessment of the potential for resistance to develop to:

- The trait (e.g., insects are no longer controlled by the trait)
- A control product that is used in conjunction with the trait (e.g., weed population no longer controlled by a herbicide used with a herbicide tolerant trait)

Development of plans for incident response, resistance monitoring, and resistance mitigation are also included. Because resistance decreases the utility and sustainability of the trait, IPM plans/programs should have a global framework with the flexibility for regional and local considerations and implementation.

[1] These include product discontinuation and incident response.

Abbreviations/Acronyms

ETS	Excellence Through Stewardship
HRM	Herbicide Resistance Management
IPM	Integrated Pest Management
IRM	Insect Resistance Management

Definitions

Herbicide Resistance Management (HRM; also known as Weed Resistance Management): A program including actions taken to delay the development of resistance to weed control measures in target weed populations.

Integrated Pest Management (IPM): A program that includes "the careful consideration of all available pest control techniques and subsequent integration of appropriate measures that discourage the development of resistant pest populations and keep pesticides and other interventions to levels that are economically justified and reduce or minimize risks to human health and the environment. IPM emphasizes the growth of a healthy crop with the least possible disruption to agro-ecosystems and encourages natural pest control mechanisms."[2] Insect Resistance Management (IRM) and Herbicide Resistance Management (HRM) are components of IPM.

Insect Resistance Management (IRM): A program including actions taken to delay the development of insect resistance to pest control measures in target pest populations.

Natural Control Mechanisms: Reduction of pest populations through the use of natural predators, parasites or pathogens.

Format of this Guide

An organization may be involved in one or more activities associated with the development and commercialization of a biotechnology-derived trait in a plant product where there is potential for development of resistance. For example, an organization may limit its activities 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 activities, this Guide has been developed as a series of informative educational sections, one for each type of resistance management (e.g., insect, herbicide) that can be adapted to the specific activities pertinent to the organization's own operations and regulatory requirements. Common to all of the sections is an emphasis on product sustainability through incorporation of resistance management strategies in product development and commercialization. The organization can adopt the sections that are applicable to its own individual circumstance. Each section covers activities with shared operational and regulatory considerations.

[2] International Code of Conduct on the Distribution and Use of Pesticides, FAO, November 2002.

The guidance in this document is intended to be flexible and its application will differ according to an organization's policy, industry initiatives, regulatory requirements, geographical scope, and type of product involved.

This Guide currently contains the Insect Resistance Management section and will be updated to include the Herbicide Resistance Management section in the near future.

Insect Resistance Management (IRM)

IRM Introduction

Insect Resistance Management (IRM) is a component of Integrated Pest Management (IPM) and requires a diverse set of tools and practices that are best identified and determined based on local farming operations and cultural practices. The IRM plan should be flexible and regularly updated based on current information such as changes in growing conditions, pest pressures and biology, product use patterns, and early indications of developing resistance to ensure the continued effectiveness of the IRM program. Insect resistance for purposes of this Guide is defined as resistance to biotechnology - derived plant products (i.e., insect protected products) as opposed to chemistry or agricultural practices.

IRM Stewardship Activities

There are a number of activities that an organization should consider in developing an IRM program. Not all of the activities outlined below may be applicable or necessary for all organizations or products in each geographic area. Appropriate functions within an organization (e.g., stewardship, biology, marketing, legal, licensing, production, regulatory, research, supply chain, communications) should be consulted in the process of designing an IRM program that includes activities to meet the specific needs of its products and intended use and geography.

Resources

CropLife International (http://croplife.org/plant-biotechnology/stewardship-2/resistance-management/)

- CropLife International - Practical Approaches to Insect Resistance Management for Biotech-Derived Crops (http://d1jkwdgw723xjf.cloudfront.net/wpcontent/uploads/2014/04/Practical-Approaches-to-Insect-Resistance-Management-for-Biotech-Derived-Crops.pdf)

Graham P. Head and John Greenplate. 2012. The design and implementation of insect resistance management programs for Bt crops in **GM Crops and Food Biotechnology in Agriculture and Food Chain 3:3, 1-10. www.landesbioscience.com** (https://www.landesbioscience.com/journals/gmcrops/2012GMC0001R.pdf)

Insect Resistance Action Committee (http://www.irac-online.org/)

- IRAC Biotechnology Web Page (http://www.irac-online.org/teams/biotechnology/)

Abbreviations/Acronyms

BMP	Best Management Practices
ETS	Excellence Through Stewardship
IPM	Integrated Pest Management
IRM	Insect Resistance Management
PUG	Product Use Guide
TUA	Technology Use Agreement

Definitions

Dose: The level of control of a target insect pest provided by an insect protected product.

Integrated Pest Management (IPM): A strategy that includes "the careful consideration of all available pest control techniques and subsequent integration of appropriate measures that discourage the development of resistant pest populations and keep pesticides and other interventions to levels that are economically justified and reduce or minimize risks to human health and the environment. IPM emphasizes the growth of a healthy crop with the least possible disruption to agro-ecosystems and encourages natural pest control mechanisms."[3] IRM and WRM are components of IPM.

Insect Resistance Management (IRM): A program including actions taken to delay the development of insect resistance to pest control measures in target pest populations.

Pyramiding: A special case of gene stacking where at least two modes of action against the same target pest(s) are provided by two or more genes combined in a single genotype.

Refuge: Host plants that do not contain the specific insect protection trait allowing a portion of the target pest population to escape exposure so that susceptibility to the trait can be maintained in the population.

Resistance: A genetically heritable change in a target population that arises from exposure of the population to the insect protection trait in the field and reduces the sensitivity of the population to the trait.

Stacking Genes: Inserting two or more transgenes into one crop which may express different traits.

Target Pest(s): Pest(s) in a cropping system that are most economically damaging and are targeted by an insect protection trait.

Trait: A genetically determined characteristic.

[3] International Code of Conduct on the Distribution and Use of Pesticides, FAO, November 2002.

Module 1 Risk Assessment

(Suggested Timing: Product concept through three or more years prior to proposed product launch)

The product concept for a new insect-protected product will guide the organization in defining product attributes based on the IRM strategy. This initial phase involves activities related to a resistance risk assessment of the particular crop/insect control trait(s) combination with regard to the intended agricultural geography where it is to be produced and commercialized. These activities include:

• Identify individual(s) in the organization responsible and accountable for IRM

The individual(s) responsible for IRM should have sufficient knowledge and experience regarding insect resistance. The primary role is to coordinate effectively the functions (e.g., stewardship, biology, marketing, legal, licensing, production, regulatory, research, supply chain, communications) in the organization to develop and ensure implementation of an IRM program and to be a point of contact (subject matter expert) for groups internal and external to the organization. In addition to the primary point of contact, there should be assigned responsibilities and authorities for implementation of the IRM plan/program and handling of changes to the plan/program throughout the product life cycle.

• Identify the intended geography and existing pest management programs

During the development of an IRM plan, identify the geography in which production and commercialization of the product is proposed and assess the local agronomic practices. The assessment will guide the organization in determining the components of an appropriate IRM plan. Considerations include:

- Geographic distribution of farm sizes
- Intercropping, monocultures and/or crop rotation
- Projected product adoption levels
- Expected level of adherence with refuge requirements and configuration
- Local agricultural economic drivers (e.g., spectrum from subsistence to industrialized)
- Local growers' current experience or history with insect protected crops
- Ability to influence and monitor grower behavior with respect to IRM
- Products offered and volumes, including products or crops with similar traits or offered by competitors
- Existing insect protected crops with similar or different modes of action
- Availability and current recommendations being used for insect control prior to trait use
- Expected shift from effective chemistry to biotechnology-derived insect protected product(s)
- Cultural (e.g., crop rotation) and biological control tools

• Identify regulatory requirements and industry guidance for intended geographies

During the development of an IRM plan, identify and address the regulatory requirements of the geography for which production and commercialization is planned. In addition to regulatory requirements for an IRM plan, industry initiatives and regional or local IRM initiatives should also be considered when determining an appropriate IRM plan.

• Identify biology and ecology of major pests to be controlled by insect resistant trait

Defining the intended use of an insect protected product will help an organization assess appropriate IRM requirements. With the identification of the target pest(s), the organization can determine the appropriate scope of IRM requirements and plan through consideration of items such as:

- Number of insect generations/growing season
- Stage(s) of insect life cycle responsible for damage
- Alternate crop and non-crop host utilization and distribution
- Adult movement and mating behavior
- History of resistance in target pest(s) and related pests
- Genetics of resistance and exposure to existing insect resistant crops, if any
- Cross crop IRM requirements

• Identify key stakeholders

It is important to develop a communication plan to engage with various stakeholders who are directly affected by, and/or have the ability to influence the IRM plan development and implementation. Different stakeholders (e.g., licensees, government regulators, grower associations, trade associations, local academic/scientific experts, crop consultants, and food and feed value chains) may need to be consulted and/or provide different types/levels of information at different times.

• Establish and implement procedures for record keeping and documentation

Policies and procedures for records and documentation are critical components of an IRM program. Documents and records may be printed, electronic, video, or other media. Examples of documentation may include:

- Reviews on agricultural systems and biology of key target pest(s)
- Results of the risk assessment

Other considerations for records include:

- Relevant and readable
- Controlled to maintain content integrity
- Clearly and consistently identified
- Reviewed in a timely manner
- Maintained according to an organization's record management policy
- Retrievable
- Deployed to appropriate users
- Secure

Module 2 IRM Plan Development

(Suggested Timing: Two or more years prior to proposed product launch)

During the second phase of IRM plan development, activities related to defining and exploring IRM options should be conducted utilizing the information gathered during the Risk Assessment (Module 1). These activities include:

• Evaluate the product performance of the trait

Key considerations in evaluating the product performance of a trait to be utilized in the development of an IRM plan include:

- Level of control at the economically important life stages of each target pest
- Dose level (in terms of insect control) of the plant or target plant parts (e.g., roots, leaves) over the crop development stages when target insect feeding occurs
- Probable use of alternative measures (e.g., insecticides to provide supplemental control) if control of target pest is not considered complete or near complete

If conducting field trials to evaluate the product performance of the trait, there may be additional regulatory requirements pertaining to the trials, depending on the geography and the regulatory status of the product (see Module 3 of the ETS Guide for Maintaining Plant Product Integrity).

• Establish baseline susceptibility for key target pest(s)

To monitor the changes in susceptibility to the control proteins, organizations should measure the baseline susceptibility of key target pest(s) populations to the trait across the growing region and these should be completed prior to widespread planting on insect protected crops. Considerations include:

- Frequency of monitoring
- Sampling methods
- Testing protocol

• Develop IRM requirements based on product characteristics and prior pest management practices

An IRM plan should be developed considering the available science as well as any other constraints that were identified, including:

- Pyramiding (stacking) multiple insecticidal traits (with different modes of action) versus single insecticidal traits
- Refuge management
  - Planning
  - Planting
  - Recording
- Maximum percentage of planting areas
- Additional IRM tools (e.g., BMPs) to complement refuge, which include:
  - Scouting and applying insecticides appropriately (differential management of the biotechnology-derived insect protected crop and refuge may be needed)
  - Limiting the use of multiple crops with the same protein(s) to control the same pest(s)
  - Cultivation
  - Destruction of crop residues
  - Crop rotation

- Seed treatment

- Regulatory submissions (in some countries the IRM plan must be provided to the regulators for review)
- Consider value of aligning IRM approaches for products with similar attributes

• Evaluate refuge options

Factors to be considered include:

- Attributes of refuge relative to the product, such as compatible agronomic characteristics of plant size, maturity group, and crop cycle
- Relative size of refuge
- Placement of refuge
- Agronomic management of refuge (fertilizer, irrigation, pesticide applications)
    - Compatibility with current pest management and agronomic practices
    - Harmonize refuge options within a comprehensive IPM plan
- Contribution of alternate host crops or natural vegetation
- Industry guidance on refuge
- Regulatory requirements for refuge
- Deployment options for refuge (e.g., blended products; co-packaging)
- Likelihood that growers will comply with IRM requirements
    - Ways to enhance compliance
    - Practicality of refuge
- Planning for refuge seed availability and distribution, by organization developing trait or by agreement with another organization

• Develop strategies to evaluate effectiveness of the IRM plan

This strategy should consider evaluation of the effectiveness of program and plan components such as:

- Product performance
- Insect resistance monitoring
- Grower compliance programs (with refuge and BMP guidelines)
- Education and training

The strategy should consider both regulatory and industry requirements and recommendations, and address how changes will be incorporated into the plans, when required. Alignment with all other applicable industry members (trait providers and chemistry providers) when developing the strategy should be considered.

• Communicate with key stakeholders

The development and implementation of a communication plan for IRM is recommended to ensure the program supports product sustainability. The communication plan provides an opportunity to receive input from various stakeholders as well as communicate resistance management plans for the new

product. Different stakeholders (e.g., licensees, government regulators, grower associations, trade associations, local academic/scientific experts, crop consultants, employees, and food and feed value chains) may need different types/levels of information at different stages. Communication/outreach to stakeholder groups often begins during the pre-commercial scale-up of the product and can continue throughout the remainder of the product life cycle.

- **Establish and implement procedures for record keeping and documentation**

Policies and procedures for records and documentation are critical components of an IRM program (see Module 1 for more detail). Examples of documentation may include:

- Refuge seed availability plan
- Product-specific IRM needs
- Communications with stakeholders

Module 3 IRM Plan Implementation

(Suggested Timing: One or more years prior to proposed product launch)

During this phase, the IRM plan should be integrated into the business activities. Key activities conducted during this phase include identifying sufficient resources (e.g., budget, employees), communicating the IRM plan, training stakeholders, including growers, and ensuring the availability of appropriate refuge seed. The activities include:

- **Develop and implement market deployment strategy by region/geography**

IRM stewardship activities, including education, monitoring for technology adoption and compliance with refuge requirements, and promotion of Best Management Practices (BMP) should be integrated into the local commercial business model and activities. Specific consideration should be given to activities that would help to enhance and promote compliance with the IRM plan such as:

- Delivery of refuge
  - Blended products (e.g., seed mix) where biotechnology-derived insect protected seed and refuge seed are combined within a single bag for the purposes of IRM when allowed by local law
  - Co-packaging (e.g., Bag in Bag) where the refuge seed is provided in a smaller package along with the biotechnology-derived insect protected seed when allowed by local law
  - Refuge sold separately
- Availability of Refuge Seed
  - Refuge seed is included in supply chain plan and is available to growers in the geography and market where the trait is being sold
  - Organization selling trait ensures sufficient, appropriate refuge seed available from their organization or other organization(s) in the geography
- Local commercialization plan, web site, brochures, customer care
  - May consider additional activities to enhance compliance with IRM requirements such as incentivize sale (e.g., seed dealers, sales representative) and use of refuge (e.g., growers)
- Farm visits to measure and understand grower adoption of IRM requirements

- **Develop and implement education/training programs**

Education/training programs should be developed and implemented for key stakeholders specific to their role in the IRM plan. Education/training tools may include:

- Product use guides
- Technology user agreements
- Development of tools to promote and manage IRM
  - IRM calculator (e.g., http://refuge.irmcalculator.com/)
  - Website (e.g., http://www.irac-online.org/)

Examples of key stakeholders that may require education/training include:

- Growers
- Internal employees
- Licensees
- Retailers

- **Communicate broadly and transparently regarding IRM plans and implementation, including tools, specific to the product**

- Employees -

An internal communication plan for personnel involved in implementation of the IRM plan should be developed that provides information regarding the importance of IRM, the key requirements of the product-specific IRM plan, regulatory implications (if applicable) and consequences of non-compliance with refuge requirements.

- Distributors, retailers, growers and licensees -

The development and implementation of a communication plan that includes training for growers, distributors, retailers and licensees for IRM stewardship is crucial for guiding and informing these stakeholders of requirements associated with the product that they must fulfill. Communication and training may be accomplished through various formats such as grower meetings, messaging at retailers, customer mailings, product labeling, Technology Use Agreement (TUA), Product Use Guide (PUG), and /or website**.**

- Other stakeholders -

The implementation of a communication plan for IRM stewardship is recommended for guiding and informing stakeholders. Different stakeholders (e.g., government regulators, grower associations, trade associations, chemistry providers, local academic/scientific experts, crop consultants, and food and feed value chains) may need different types/levels of information at different stages. Communication/outreach to stakeholder groups often begins during the pre-commercial scale-up of the product and can continue throughout the marketing phase.

- **Assess initial IRM implementation efforts**

The organization should have systems in place, in order to assess the initial IRM plan implementation and effectiveness of the education activities. During this assessment, feedback from growers, employees, regulators and other key stakeholders should be evaluated and appropriate modifications to the IRM plan should be considered.

- **Establish and implement record keeping and documentation procedures**

Policies and procedures for records and documentation are critical components of an IRM program. Examples of documentation may include:

  - Training and communications materials
  - Plans for refuge seed supply
  - Assessment of initial IRM implementation efforts (change management)

Other considerations for records can be found in Module 1.

Module 4 IRM Program Maintenance and Compliance with IRM Requirements

(Suggested Timing: Product launch through product discontinuation)

The activities that are conducted at this phase support ongoing stewardship to ensure continuing compliance to the IRM plan and to monitor for issues which may require action, including adjustments to the plan. These activities include:

- **Establish and implement monitoring procedures for:**

  - Adoption and use patterns -

  One of the key components of the risk assessment used to determine the IRM plan was the assessment of current agronomic practices (A. Risk Assessment). As the agronomic practices/patterns change, the effectiveness of the IRM plan can be affected. Therefore, it is important for an organization to monitor the technology adoption levels and changes in agronomic use patterns and practices (e.g., alternate hosts) and make necessary changes to the IRM plan to improve effectiveness. If there is more than one trait provider, collaboration with the other applicable industry members to conduct monitoring should be considered.

  - Compliance with refuge and other IRM requirements (including BMPs) -

  In order for an organization to assess compliance with the IRM plan, programs should be in place to monitor compliance with refuge and other IRM requirements particularly if a structured refuge is part of the plan. Monitoring activities to assess compliance with IRM requirements may include grower surveys coupled with in-field inspections. Depending on the regulatory requirements, this monitoring may be mandatory or voluntary. Considerations include:

    - Developing a plan to work with customers who have not complied with the IRM requirements. This plan may include additional education and assistance or denied access to the technology in subsequent seasons.
    - Refining educational programs based on compliance with refuge requirements.
    - Reviewing the IRM requirements to determine if they can be made more flexible or practical without compromising their effectiveness.

○ Resistance monitoring -

It is important for an organization to implement procedures to monitor for changes in target pest susceptibility to the product. This type of monitoring will inform the organization of any changes in product efficacy that may require changes to the IRM plan. Considerations include:

- Baseline studies
- Pest susceptibility studies which may include one or more of the following:
  - Laboratory feeding tests with purified or semi-purified proteins
  - Standardized lab or greenhouse testing of insects against plants expressing the trait
- Assessment of technology's performance in the field including evaluation of efficacy
- Process for investigating performance inquiries including collection and bioassay of target insects when appropriate and possible
- Monitoring secondary/minor pests as their population can increase as a result of the decrease in the target pest(s) population(s)

If there is more than one trait provider, collaboration with the other applicable industry members to conduct monitoring should be considered.

- **Establish and implement procedures for:**

○ Complaint handling or non-compliance with refuge requirements -

The organization should have procedures in place to address grower complaints as well as any concerns that are identified through the course of the various monitoring procedures as described above. Key considerations to include are:

- Tracking complaints and non-compliance with refuge requirements
- Communication plan for:
  - Follow-up with growers/ customers
  - Changes made to the IRM plan

○ Mitigation Plans -

- Process for investigating performance inquiries
- Update the IRM plan to manage any potential insect resistance development and align with industry initiatives when applicable
- Refine educational programs

○ Regulatory reporting requirements -

Depending on the geography and regulatory requirements, there may be reporting requirements (e.g., resistance monitoring, compliance monitoring) that must be fulfilled. A process should be established to handle the reporting requirements.

○ Record keeping and documentation -

Policies and procedures for records and documentation are critical components of an IRM program. Examples of documentation may include:

- Insect resistance baseline and monitoring for resistance
- Compliance with refuge requirements

- Reports of potential resistance
    - Include the final status of the potential resistance follow-up (e.g., not resistant, confirmed resistance)
- Product adoption and use data

Other considerations for records can be found in Module 1.

Herbicide Resistance Management (HRM)

Under Development