SABIMA

Strengthening capacity for safe biotechnology management in Sub-Saharan Africa

A project of the Forum for Agricultural Research in Africa (FARA)

Biotechnology Stewardship Training 2009 – 2010

Trainer's Syllabus

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1. Introduction

In 2008, 125 million hectares of genetically modified crops were cultivated in 25 countries around the globe (James, 2008[1]). Due to the economic, environmental and welfare benefits offered by biotech crops for both large and resource poor small farmers this growth trend in adoption is expected to continue.

Biotech crops are not new to Africa. Bt corn has been grown commercially in South Africa since 1996. In 2008 1.6 million hectares of Bt and herbicide tolerant maize were grown there (62% of the total country maize cultivation). Also 80% of the 230,000 hectares of soybean were genetically modified (Karembu et al, 2009[2])

The interest in the benefits that biotech crops can contribute towards food security is gathering pace. Over 30 African governments are developing biosafety legislation and regulatory frameworks. In 2008, for the first time Burkina Faso commercialised Bt cotton and Egypt approved Bt corn. There are many active research and development programmes in countries such as Kenya, Uganda, Nigeria, Ghana, Malawi, Tanzania, Mozambique and Burkina Faso. There are over 35 trait events under investigation in more than 10 food crops. The increasing scale of research and development and the advancement of biotech products towards commercialisation, means that the creation, implementation and continuous improvement of the best agricultural biotechnology stewardship practices are an imperative for Africa.

1.1. Challenges to bringing a biotech product to the African market

1.1.1. Unique challenges

Biotechnology developers and users share their interest in promoting the responsible use of agricultural biotechnology, whilst delivering maximum benefits for farmers and the whole value chain. Since the first global product introductions in the mid 1990s, private sector developers have become increasingly aware of the need to implement and continuously improve their quality management and stewardship programmes for the full life cycle of their biotech plant products. Much has been learnt in the last 10 years and some of the key stewardship challenges include:

- **Safety** Due to the precautionary principle, developers must address the broadest range of human, animal and environmental safety questions, which go much beyond those required for products from conventional breeding. Integration of safety elements in the design of the product, documenting safety throughout development, compiling state-of-the-art scientific data packages and obtaining endorsement by experts of safety assessments are just a few activities that are required for products of biotechnology.
- **Detection capacity** Breeders must deliver specified levels of varietal purity as a mark of quality and are expert in achieving these in their breeding and plant/seed production routines. For some crops these have been formalised in internationally accepted standards (*e.g.* OECD seed certification schemes) However, the uniqueness of genetic modifications combined with highly sensitive molecular tools allow detection of the presence of biotech traits to an unequalled level of sensitivity. Whereas standard breeder's practices guarantee deviation of purity by a few percent, molecular techniques can easily identify with high certainty presence of unintended material down to parts per million. This level of detection requires a different set of norms to be used within the seed industry.

[1] James, Clive. 2008. Global Status of Commercialized Biotech/GM Crops: 2008. *ISAAA Brief* No. 39. ISAAA: Ithaca, NY.978-1-892456-44-3

[2] Karembu, M., F. Nguthi and H. Ismail (2009) Biotech crops in Africa: The final Frontier, ISAAA Africentre, Niarobi, Kenya.

- **Regulatory frameworks** Plant biotechnology is heavily regulated both at national and international level. Most regulatory approaches start with a prohibition and only allow activities upon a formal notification and/or approval following review of hazard and risk information. Furthermore activities may be subject to certain conditions such as integrated pest management and refugia schemes. Unapproved activities or failure to respect all conditions lead to regulatory actions, loss of reputation and can result in important fines, mitigation programmes and public blame affecting corporate image.
- **Scientific collaboration** Scientific research has never relied so heavily on international interactions across the globe. As research groups specialise in advanced technologies, materials and information are exchanged at an increasing frequency. Genetic elements coming from very different sources can be combined in a genetic construct used in plant transformation experiment and yielding several events. The selection and breeding occurs in greenhouses and field trials. Each of these steps can happen at different locations, requiring very different competencies and working environments. For all the collaborating parties it is crucial that each individual party maintains a high level of quality management and stewardship.
- **Trade** Conventionally bred crops are provided to farmers, who use and sell the harvest of their fields. In some cases integrated systems have been developed. However, direct communication remains limited to a few parties in the product chain. For agricultural biotechnology products this communication has been dramatically broadened and developers regularly need to interact with processors, retailers and consumers. As many of the products become part of international trade, also downstream users in other countries need to be engaged.
- **Public attention and NGOs** Development of biotechnology attracts a lot of public attention. Scientists highlight their achievements and potential of the technology. NGOs voice concerns on potential impact and societal issues. Some organisations have very strong negative opinions and media magnify their scaremongering stories, even though there may be no scientific foundation for raising public concern.

Some NGOs diligently watch for opportunities to allegedly demonstrate that technology cannot be contained or controlled. One example is the "GM Contamination Register", an initiative of GeneWatch UK and Greenpeace International to record all incidents of contamination arising from the intentional or accidental release of genetically modified organisms. Their database[3] includes:

- **Contamination incidents** Food, feed or a related wild species have been found to contain unintended GM material from a GM crop or other organism
- **Illegal plantings or releases of GM organisms** When an unauthorised planting or other release into the environment or food chain has taken place

1.1.2. Case study: Starlink™ Corn

Private sector experience has demonstrated that there is a compelling need for excellent stewardship programmes and standards to be in place during the product full life-cycle from product inception through research, development, commercialisation and discontinuation. Case studies on products are a very helpful tool to assimilate best practice.

The information on this case study is taken from the US Environmental Protection Agency (EPA) website[4] and the March 2008 U.S. EPA White Paper "concerning

[3] www.gmcontaminationregister.org
[4] http://www.epa.gov/pesticides/biopesticides/pips/starlink_corn.htm#proposal

dietary exposure to cry9c protein produced by Starlink™ Corn and the potential risks associated with such exposure"

StarLink™ refers to a variety of yellow corn genetically engineered to express the protein Cry9C, which is toxic to various insect pests of corn and acts as a pesticide (a plant-incorporated protectant). During the mid-1990s, the registrant, Aventis Agroscience, Inc., submitted data to EPA on the safety of StarLink™ and applied for necessary approvals under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA).

After reviewing the available data, EPA was undecided whether the Cry9C protein was a potential human allergen. All other information indicated that Cry9C would not pose any other types of risks to human health or the environment. Accordingly, in 1998, EPA registered StarLink™ for commercial use, provided that all grain derived from StarLink™ corn was directed to domestic animal feed or to industrial uses (*e.g.*, biofuels). The intent of requiring all StarLink™ to be segregated as either domestic animal feed or for industrial use was to preclude any occurrence of the potentially allergenic Cry9C in human food. The registration contained several specific requirements designed to ensure that no StarLink™ grain would enter the human food supply.

Following registration, relatively small quantities of StarLink™ were planted in the United States: 9,018 acres in 1998; 247,694 acres in 1999; and 350,000 acres in 2000, with the largest planting representing less than half a percent of the total acreage planted to corn in the United States. (Approximately 70 to 80 million acres of corn were planted in the U.S. in 1998 through 2000.)

In September 2000, residues from StarLink™ were detected in taco shells, indicating that it had entered the human food supply. In response to these detections, Aventis requested cancellation of the StarLink™ registration, and the Food and Drug Administration (FDA) recommended that dry grain mills processing yellow corn test for the presence of Cry9C.

When instituted in 2000, the monitoring programme recommended by FDA resulted in the identification and diversion of numerous shipments of corn testing positive for Cry9C to domestic animal feed or industrial uses. From 2000 onward, millions of bushels of grain had to be redirected as a result of the StarLink™ containment program. These actions reduced the levels of Cry9C in the human food supply and lowered the likelihood that, if StarLink™ derived Cry9C were a human allergen, any individual would receive enough exposure to become sensitized, and that, if any person did develop an allergy to StarLink™ derived Cry9C, the sensitized individual would not be exposed to sufficient levels of the allergen to produce an allergic response.

More than 4 million tests on 4 billion bushels of corn were performed from the time FDA first issued its recommendations until 2007. Since 2003 there has not been a verified positive test of yellow corn for dry milling in the marketplace. Consequently in 2008 EPA recommended that further testing of corn grain for Cry9C at dry mills and masa operations was not necessary.

The StarLink™ case is one of the examples illustrating the damaging set of consequences if a product of biotechnology ends up in a product stream for which it is not intended, including not least:

- Product channelling to avoid further commingling with mainstream products,
- Food product withdrawal of high profile brands in the US from market shelves and major financial losses,

- Major costs to cover all the detection testing and monitoring of grain supplies,
- Fines and court cases,
- Interruption of international trade of corn to importing countries,
- Loss of confidence by the public in the government regulatory agencies, grain traders, food processors and food companies, and
- Reputational damage for the developer.

All this damage occurred because the grain and food supply chain contained a trait unregistered for food consumption. It is worth remembering that it was never proven that Cry9C posed a real human safety risk, but the potential risk and clearly unauthorized presence was sufficient to cause a major chain reaction in trade.

1.2. Quest for an internationally adopted stewardship system

Ensuring quality control and responsible management of the technology has been central to developing and commercializing new biotech crop varieties. Stewardship makes good business sense - careful attention to the safety of products and their market impact is essential for high value products in any industry. In agricultural biotechnology, meticulous production methods are a business requirement so the seeds sold will yield harvests with the desired characteristics, and environmental sustainability. This is an essential step to providing more and better food, feed, and fibre through agricultural biotechnology.

As the first commercial developments were managed by industry, they were also first to face the stewardship challenges. Over the years several position papers and guidance documents were developed that summarized the experience of the developers in specific areas, *e.g.* Insect Resistance Management, Field Trial Compliance Manual/Workshops, Containment Analysis and Critical Control Point (CACCP) Plan and Product Launch Stewardship Policy.

In 2002 BIO, the world's largest biotechnology organization, providing advocacy, business development and communications services for more than 1,200 members worldwide, and its members formed a "Beyond Compliance Taskforce" to formally leverage industry's experience to educate a wide audience of users on best practices for product stewardship.

In 2007 this was further formalised with the launch of a new program, "**Excellence Through Stewardship**" (ETS), the first industry-coordinated effort to address product stewardship and quality management. The program's three main components include:

- Stewardship Objectives, Principles and Management Practices, which members are required to adopt and abide by to contribute to responsible product management.
- Guides to Understanding and Implementing Stewardship and Quality Management Systems, which promote stewardship and quality management practices for the responsible use of biotechnology-derived plant products globally.
- A Global Stewardship Audit Process, which involves third-party audits of members to verify that stewardship programmes and quality management systems are in place.

The mission of the ETS initiative is to **promote the responsible management of plant biotechnology, primarily by developing and encouraging implementation of product stewardship practices and by educating the public about those practices.**

As illustrated in this review, the elaboration of general stewardship concepts in plant biotechnology is still very recent. Furthermore, it is mainly based on experience achieved by industry in mostly industrialized agricultural markets. As more research for African crops and in African institutes reaches first field releases and subsequent development steps are contemplated, the stakeholders involved can benefit maximally from the acquired experience while ensuring adaptation to the specific characteristics of their products and markets.

1.3. The SABIMA project

The Forum for Agricultural Research in Africa ("FARA") is a public organization with head office in Accra, Ghana, that is committed to the increase in agricultural production and poverty reduction through the implementation of the AU-NEPAD Comprehensive Africa's Agricultural Productivity ("CAADP") Pillar IV which address research, technology dissemination and adoption. FARA's Mission is to create broad-based improvements in agricultural productivity, competitiveness and markets by supporting the Sub-Regional Organisations ("SROs") in strengthening Africa's capacity for agricultural innovation.

FARA, through a grant from the Syngenta Foundation for Sustainable Agriculture, is leading a 3 year project on "Capacity Strengthening for the Safe Management of Biotechnology in Sub-Saharan Africa" ("SABIMA"). The SABIMA project is oriented to promoting and supporting the need for Africans to develop the skills, processes and capacity for stewardship of biotech products right through the entire value chain from research to product development, seed production, testing and marketing. The project is implemented by the SROs and the National Agricultural Research System ("NARS") in six countries in Sub-Saharan Africa: Burkina Faso, Ghana, Nigeria, Kenya, Uganda and Malawi. These countries have been selected individually because they have research and development projects using transgenic plants that are expected to progress towards commercialisation.

The specific objectives are to:

- Update information on the current status of agricultural biotechnology and biosafety in these six countries in Africa. This includes creating a database of human resources, laboratory infrastructure and research, development and technology transfer activities as well as biosafety legislation and stage of implementation.
- Identify the capacity building gaps in these countries and the modalities for intervention.
- Provide training in stewardship in FARA, the SROs and the NARS of the selected countries.
- Identify and train stewardship leaders in FARA, the SROs and focal persons/champions in stewardship to ensure sound stewardship programmes are implemented and fully operational, and to become stewardship advocates with stakeholders.

This syllabus is part of the stewardship training of the SABIMA project. It is intended as an educational tool and a reference document for those that successfully conclude the training and are recognised as FARA stewardship trainers.

It provides guidance to assist users in developing and implementing their own organization-specific stewardship process for plant biotechnology products. The introduced approach is flexible and its application will differ according to the size, nature and complexity of the organization and products involved. The syllabus is representative and not exhaustive. It is the responsibility of anyone using this approach to consider the specific organization by which the stewardship effort will be

implemented and the applicable legal requirements. Although the principles remain, each effort will need to be tailored.

The recommendations in this document should not be used as a substitute for

- A user's own individual understanding of legal requirements,
- Consultation by a user with its legal counsel and other advisors, or
- Direct contact with appropriate regulatory agencies.

Two types of training are provided:

- **Stewardship background:** This background training is for people in management and research, who need to understand the importance and implications of stewardship, but who rely on colleagues or staff members for the operational development and implementation of the programme.
- **Stewardship trainers:** This is a detailed training for individuals who will be responsible for developing, implementing and communicating stewardship inside and outside of their organisation. The training was organised in different modules, each addressing a particular aspect of a stewardship programme. Only those that participated in all modules and that completed the assignments were qualified as FARA stewardship trainers.

The stewardship training participants were nominated by the Director of their organisation and were identified before the start of the training. They must also have the support of their management to be able to contribute to the development and implementation of stewardship processes in their organisation after completion of the training. There were no specific educational requirements, but participants were expected to be familiar with the basic concepts in plant biotechnology. These include concepts from molecular biology as well as agronomy. They also had to be familiar with regulatory requirements that are applicable to biotech activities and products.

The training was organised by Dr. Patrick Rüdelsheim. After being in charge of Biotechnology Regulatory Affairs in respectively Plant Genetic Systems N.V., AgrEvo, Aventis S.A. and Bayer, he founded and became General Partner of Perseus BVBA, a service company focused on bio-safety and related regulatory requirements. Over almost 20 years he accumulated experience in regulatory support of GM products, field trials and commercial releases and has been involved in different projects in Africa. He followed the introduction of the "Excellence through Stewardship" initiative; the first industry based initiative for stewardship of GM crops, and provided the 2009 training of auditors. He was nominated by the Belgian authority as an expert for the Roster of Experts of the Biosafety Clearing House.

2. Stewardship in biotechnology

2.1. What is Stewardship?

Stewardship is the careful and responsible management of something entrusted to one's care. It refers to the way we manage something rather than to what we actually manage.

While several documents on stewardship in biotechnology exist, the most comprehensive approach today is the Excellence Through Stewardship ("ETS") programme, launched in 2007 by BIO. It is the first biotechnology industry-coordinated initiative to promote the global adoption of stewardship programmes and quality management systems for the full life cycle of biotechnology-derived plant products.

In ETS terminology stewardship in plant biotechnology is **the responsible management of a product from its inception through to its use and discontinuation.**

ETS sets the following objectives for their Stewardship Programmes:

- Fully comply with applicable regulatory requirements.
- Seek to achieve and maintain plant product integrity.
- Work to prevent trade disruptions in order to facilitate the flow of goods in commerce.

In line with ETS recommendations, the following listing of programme components should be considered and appropriately incorporated at each phase of the product life cycle when developing new stewardship programmes or improving existing programmes:

- The organization's structure, including defined roles and responsibilities, focused on maintaining and improving stewardship policies and practices to ensure accountability across all global regions.
- Stewardship policies, processes and procedures integrated with quality management systems.
- Stewardship awareness and training programmes for employees, contractors, co-operators, licensees and growers.
- Established communication networks for dissemination of information internally and externally to stakeholders.
- A process for maintaining plant product integrity.
- Defined stewardship-verification processes for internal and external operations.
- A process to include stewardship and quality-management responsibilities and requirements in applicable contracts and licensing agreements.
- A policy and process for the responsible commercialization and launch of biotechnology-derived plant products.
- A process to effectively manage potential incidents involving biotechnology derived plant products.
- A process for responsible discontinuation of biotechnology-derived plant products.
- Stewardship management reviews at milestones along the product life cycle.

Organizations that want to adhere to or improve their stewardship approach need to also address the following challenges:

- To fully understand the concepts, even if they do not have experience in all stages of the life cycle of a biotech crop.
- To evaluate which aspects are and will become relevant given the scope of their activities.
- To install a robust system that will build confidence with third parties and stakeholders.
- To create awareness and buy-in of the involved staff.

Comment: Stewardship and Intellectual Property
Often the term stewardship is used to also include understanding and management of intellectual property ("IP") and contracts. The scope of the SABIMA training follows that used by ETS which does not include IP as a core focus. For the purposes of this training it is assumed that institutions will comply with National and International laws on IP and partner contractual arrangements. An organisation can decide to include IP as an element of its stewardship effort.

2.2. A programme of continuous improvement

Stewardship is not a goal per se. It is an effort pursuing an "ideal" way of working, which takes into account the different themes that are important for responsibly managing a biotech product. The best stewardship programmes are characterized by an effort of continuous improvement.

A **continuous improvement process is a management process whereby the processes are constantly evaluated and improved in the light of their efficiency, effectiveness and flexibility.** The core principle of such an improvement effort is the (self) reflection of an organization on its processes. During the improvements suboptimal processes are identified, reduced and eliminated, thus increasing efficiency. The emphasis is on incremental, continuous steps.

Many systems that are deployed today are prescriptive. They tell in detail what to do or prescribe conditions that need to be fulfilled. This approach can lead easily to losing out of sight the reason why something is done. It may result in an inappropriate execution of rules that are actually not contributing and even sometimes counterproductive to achieving the original goal.

As a consequence the stewardship approach is implemented as a management system and not a fixed process. **A management system is a set of interrelated elements used to establish policy and objectives and to achieve those objectives**. A management system includes organizational structure, planning activities (including for example, risk assessment and the setting of objectives), responsibilities, practices, procedures, processes and resources. It allows evolution over time in function of experience and new developments.

In a management systems approach one starts with clearly defining the goals, followed by detailed analysis of the necessary steps to achieve these goals. Important threats and how to avoid their realisation are mapped. During implementation, the way these planned actions and circumstances influence the achievement is controlled and where needed improvements are included. Even when the goals are achieved, the system will include routine verification in order to stay on target and to improve efficiency where possible. As such a systems approach creates a dynamic environment, involving the entire organisation and encouraging continuous improvement by all.

Stewardship is not a regulatory requirement *per se*. While a good stewardship effort will ensure full compliance with the legal requirements, the effort will also cover other aspects (*e.g.* contractual arrangements, interaction between value chain parties) that remain outside of the scope of GMO legislation. While a strong regulatory system oversees plant biotechnology, biotechnology product stewardship is the responsibility of each developer and user. It is a good way of doing business, supports mutual trust in collaborations, and improves efficiency and strengthens stakeholder and consumer confidence.

2.3. Phases in the biotech life cycle

A biotech crop product moves through different phases during its life cycle (see figure 1).

Figure 1: Schematic representation of the biotech product life cycle (modelled after the *Guide for Stewardship of Biotechnology-Derived Plant Products (March* 2009 Excellence Through Stewardship)

Although the transition from one phase to another is not always sharply delineated, each phase has some individual defining characteristics:

- **Gene Discovery phase** covers activities to identify and evaluate the specific genes and other elements that may be used to produce or construct a new plant product through biotechnology. These activities involve basic research in contained laboratory, growth room and greenhouse facilities. Occasionally a limited scale research field trial may be required. This phase typically is concluded by a proof of concept. Material developed during this phase may be suited for further development, however in most cases this basic research material may contain features that are not desired for development and commercialisation.
- **Plant Product Development phase** includes activities that occur before a biotechnology-derived plant product can be commercialized. These activities include plant transformation targeted to produce products and regeneration, event selection in contained facilities and confined field trials, and event evaluation for agronomic and regulatory studies. An important aspect is the scientific profiling of the selected event with molecular characterisation, definition of human safety and environmental impact and trait stability testing. Typically this phase also includes obtaining all the approvals required for product launch.
- **Plant/Seed Production (Multiplication) phase** is a continuous process in which plant/seed products are grown according to defined standards and requirements to ensure genetic identity, maintain varietal purity, and meet certain quality standards before distribution to growers. In many countries, seed multiplication is part of a legally sanctioned system for quality control of seed production. Generally, there are four stages of seed multiplication: breeder seed, foundation seed, registered seed, and certified seed. They may or may not be

grown under confined conditions depending on the status of the regulatory authorizations.

- **Plant/ Seed Marketing and Distribution phase** includes activities related to the distribution of product through the internal supply chain and the external distribution chains to customers. Prior to the commercial sale of any biotechnology derived plant or seed product, the product developer or its licensee should have secured all necessary regulatory authorizations as a prerequisite to market launch. Often this phase is not controlled by one entity
- **Crop Production phase** includes activities involved in the cultivation for harvest of an authorized, commercially available biotechnology-derived seed or plant.
- **Crop Utilization phase** includes the use and processing of biotechnology-derived plant products for food, feed, fibre or other purposes (*e.g.*, biofuels, industrial applications, etc.).
- **Product Discontinuation phase** includes activities involving products that were authorized for commercial use, but have since reached the end of their commercial life cycle. This activity is separate and distinct from product withdrawals or recalls. Discontinuation of a product is a business decision, and takes into account many factors, including the prevailing regulatory requirements, market forces and product replacement. Discontinuation is a normal part of the product life cycle.

2.4. Life cycle themes

During the life cycle of a biotech product many people will be involved and take care of a particular aspect. The overall goal is to develop a product that sustainably benefits the users while providing guarantees for safety in full compliance with all applicable legislations. Figure 2 shows a breakdown of this overall goal in specific themes as they are usually implemented in an organization. Stewardship promotes these themes by making them explicit during the life cycle and by offering a system that is intended to improve the efficiency in achieving these themes.

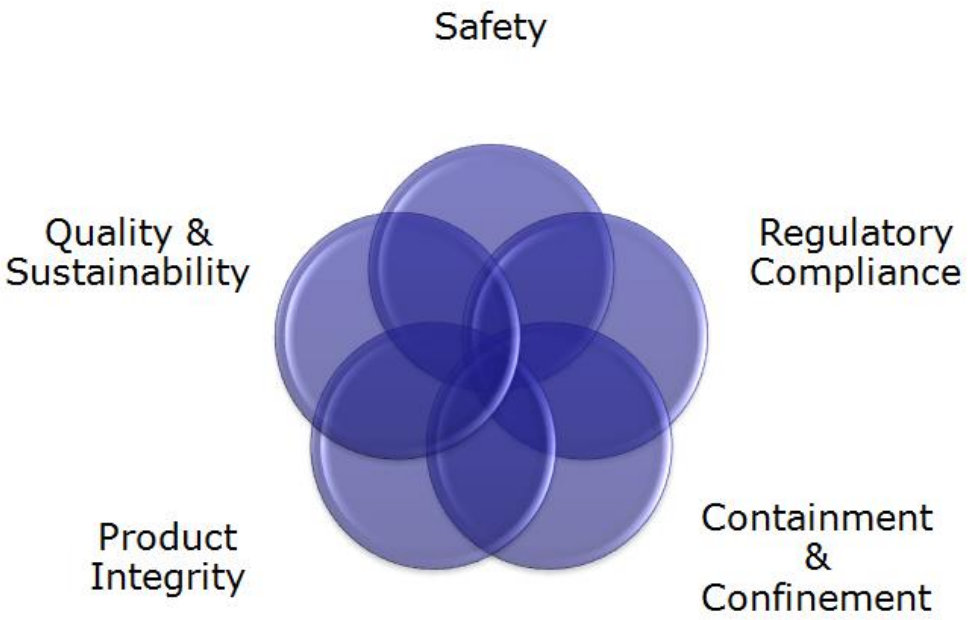

Figure 2: Schematic representation of themes that are crucial in the different life cycles of a biotech product.

While these themes are recognized as distinct for one another, there are common areas and the themes mutually strengthen each other. For instance most regulatory requirements are intended to provide guarantees for safety and are based in early phases on containment/confinement measures. Containment and confinement ensure that biotech material does not get commingled with other material, and at the same time can help to ensure product integrity.

Depending on the organisational structure different people and different departments may be involved in the realisation of a particular theme. Stewardship stresses that these efforts need to be aligned and coordinated, increasing efficiency and avoiding gaps.

2.4.1. Safety

Throughout the life cycle the concern for safety is of prime importance. The safety of the people involved in research and development needs to be guaranteed from the inception of a research project. Furthermore, only safe products have an opportunity to be accepted for field trials and commercial introduction. Safety has to be considered in terms of impacts on humans, via direct exposure or via consumption, and on the environment.

To date there have been no safety issues with genetically modified plants approved and commercially grown. Nevertheless, the precautionary principle requires a careful evaluation and if necessary management of potential risks.

From a stewardship perspective an organisation should ensure that:

- During the entire life cycle of biotech products information is accumulated to identify any safety issue.
- Only products supported by state-of-the-art safety demonstration are carried forward through development and eventually to market.
- Systems are in place to react on new findings.

Here are some examples for consideration at different phases of a product life-cycle:

- Gene Discovery - genetic elements are evaluated for factors which may impact human and environmental safety, such as the potential for allergenicity or toxicity of expressed proteins.
- Plant Product Development - In the design of constructs for plant transformation intended for commercial release and when selecting transformed plant lines for advancement during product selection, technical and regulatory implications of all genetic components including *e.g.* selectable markers, are evaluated. Also a science-based regulatory strategy is implemented to collect and analyse appropriate human safety, efficacy and environmental safety data in order to meet regulatory requirements appropriate for intended product use plans.
- Crop Production and Crop Utilization - a system is maintained of monitoring and readiness to react to new findings.

2.4.2. Quality & sustainability

Product specifications have to be determined by identifying performance criteria and setting quality acceptance levels. For instance when developing a virus tolerance crop it is important to specify what type and level of tolerance will be considered adequate. It is possible that an initial approach may provide some tolerance. However if this tolerance is suboptimal compared to the quality requirement, it is unlikely to become an attractive product. Similarly quality

parameters need to be observed for other standard characteristics of the material (*e.g.* germination rate, maturity,..) like for other plant material.

Activities are designed ensuring that the final products meet these expectations. Final products can be tested to verify if they are in accordance with the specifications.

The **sustainable use** of the product can be enhanced by implementing management strategies. For instance when working with an insect tolerant crop, one of the concerns is the development of resistance in the target insects thereby rendering the protection strategy ineffective. Programmes for insect resistance management, *e.g.* based on appropriately defined refuge strategies, are seen as key management strategies for sustainable product use. Similarly for herbicide tolerance crops, weed resistance management schemes based herbicide rotation or combination strategies, should be explored. Some examples and references:

- F.Gould and M.B. Cohen (2000) "Sustainable Use of Genetically Modified Crops in Developing Countries," Agricultural Biotechnology and the Poor Report, Consultative Group on International Agricultural Research.
- IRAC[5] IRM for Biotechnology.
- National Corn Growers Association[6]: Insect Resistance Management Fact Sheet For Bt Corn.
- Dow AgroSciences leaflet[7]: Insect Resistance Management for Bt Corn 3rd Edition.
- Monsanto[8] 2009 IRM Guide.
- Monsanto[9] 2009 Technology Use Guide.

While these references provide examples, it must be highlighted that they have been designed to be used in a specific type of agricultural setting. Some of the tools and methods that have been used, will need to be redesigned in order to fit with African agricultural practices and tradition.

It is important that both quality and sustainable use are identified early in the life cycle and that actions are taken to ensure that the product will be properly accompanied:

- Quality parameters and acceptance levels can be determined as early as the start of the Plant Product Development phase. Achieving the acceptance levels would be an important criterion during the plant selection process.
- During the entire life cycle processes are identified which can influence the performance criteria. Additional actions may be included to enhance the chance for meeting the specifications, *e.g.* perform a herbicide treatment in seed production of herbicide tolerant material. Whenever situations are identified that might influence achieving the specifications, additional measures are established to avoid that such an influence occurs. *E.g.* pre-mature harvesting may influence seed quality in certain crops. Such practices should therefore be avoided in all cases where optimal seed quality is required.
- When appropriate and feasible, testing is foreseen to evaluate if the specifications have been met. Only material meeting the specifications should be

[5] http://www.irac-online.org/Biotechnology/Home.asp
[6] http://ncga.com/insect-resistance-management-fact-sheet-bt-corn
[7] http://www.dowagro.com/pgb/commitment/product/irm.htm
[8] http://www.monsanto.com/monsanto/ag_products/stewardship/irm.asp
[9] http://www.monsanto.com/monsanto/ag_products/stewardship/tug.asp

used as planned. For other material alternative uses including destruction have to be evaluated.

- Appropriate management strategies need to be designed and developed during Plant Product Development. The information may be required to address certain regulatory requirements.
- The implementation of management strategies occurs during the Crop Production and Crop Utilisation phases. Developers will need to ensure guidance and inform users on the particular conditions of use. This includes providing appropriate communication and training regarding product management practices that enhance the long term efficacy of the product. It also requires establishing processes to capture and appropriately manage customer feedback related to product attributes or use.

2.4.3. Plant Product Integrity

Plant product integrity (PPI) is the specific identity of a plant and purity of populations of the plant that are established and maintained using appropriate measures.

During the process of introducing traits via genetic engineering, the identity and purity of the material must be controlled at different levels, including genetic elements, constructs, vector organisms, recipient material and transformation events. These levels provide a new challenge for defining identity and purity specification go far beyond what is current practice in traditional breeding. As product definition is also central to regulatory approvals, a clear and strict definition is required for all materials.

In order to ensure that all materials correspond to the required specifications of identity and purity, an assessment based on the Hazard Analysis and Critical Control Points ("HACCP") is maintained. This topic is further elaborated under point 3.2 of this document. As a result of the analysis a quality management system for maintaining plant product integrity is implemented or adapted. In this respect reference is made to the ETS[10] "Guide for Maintaining Plant Product Integrity".

Such a quality management system should address at each appropriate product life cycle phase :

- Misidentification.
- Mislabelling.
- Inadequate facilities or controls for containment.
- Insufficient isolation or other control measures that do not prevent or that limit cross-pollination of plants.
- Inadvertent physical mixing of plant material.
- Incomplete clean-out of planting, harvesting, transporting, and conveying equipment, and storage facilities.
- Errors in evaluating the transgenic purity of plant material to be planted, harvested and/or retained.
- Errors in tracking.
- Errors in disposition.

10 http://www.excellencethroughstewardship.org/facts/documents/Guide%20for%20Maintaining%20Plant%20Product%20Integrity.pdf

Involvement of third parties can be needed early in a research and development programme *e.g.* special services for field trial testing. During Plant/Seed Production, Plant/Seed Marketing & Distribution, Crop Production and Crop Utilization, a great diversity of parties will contribute to the entire value chain of the biotech product. In this respect it is important that stewardship requirements are included in contracts and licenses. This can be accompanied by implementation of stewardship awareness, training and verification programmes for contractors, licensees and growers.

2.4.4. Containment & confinement

Developers and users have a responsibility to prevent the spread of their biotech traits beyond the integrity of their own products. This can be achieved by:

- **Containment** The control of viable seed or vegetative propagating material in a manner that mitigates their release outside of their controlled development in the laboratory, greenhouse, seed-conditioning or -storage facilities. Note that also containment during storage and transport deserves proper attention.
- **Confinement** The control of viable seed or vegetative propagating material planted in the field in a manner that mitigates the spread of pollen or other propagatable plant parts out of the confined trial area.

The potential for spread of biotech traits is largely determined by the biology of the material, the specific activity and the environment in which the activity is performed. Understanding these factors and the routes of dispersal is the starting point for any design of containment measures in the laboratory, in greenhouses, in the field as well as in facilities designed for seed cleaning and storage. Dispersal is evaluated both in space (*e.g.* pollen being carried by wind over a certain distance) and in time (*e.g.* seeds remaining viable in the soil).

Strict containment is required in the Gene Discovery and early Plant Product Development phases. One of the operating principles is that exposure of the public and the environment needs to be prevented. Containment and confinement measures and proper inactivation of material before disposal are combined to this end.

A second objective is to avoid creating sources of adventitious presence or Low Level Presence. Both are forms of unintentional and accidental commingling of trace amounts of one type of seed, grain or food product with another (see glossary). As developers strive to preserve the identity and purity of their material, this will also contribute to ensure that the identity and purity of other's proprietary material is not threatened. However, this may not always be sufficient and specific measures may be required. This is relevant for other material from the same developer as well as for third party materials.

In addition to containment and confinement measures, an important element is keeping track of materials and proper agreements with any third parties that might be involved in control and fate of the materials. **Traceback refers to the ability to follow the movement of a biotechnology-derived plant through specified stage(s) of development, production, and distribution to growers.** It is a key element common to all phases. (see section 3.3.3)

When preparing for Crop Utilization, an assessment has to be made of the regulatory and stakeholder requirements and recommendations for identity and purity in grain. Although this phase is usually beyond of the control of the developer, responsible development could include the promotion of stakeholder systems for maintaining and documenting plant product integrity, inventory control and traceback.

One option is to enable third parties to do their own verifications as they see appropriate. This is achieved by providing information on the specific material and on tests that can be done to verify the presence of the biotech traits. At the same moment processes can be implemented to capture and appropriately manage stakeholder feedback related to product attributes or use.

2.4.5. Regulatory Compliance

Countries are at different stages of implementing legislation for activities with biotech products. Depending on the country, these may cover use in contained facilities, confined field trials, commercial introduction, food and feed use, import, export and internal transport.

References for this component can be found in:

- CropLife International (2005) Compliance Management of Confined Field Trials of Genetically Engineered Plants.
- BIO (2007) Confined Field Trials of Regulated Genetically Engineered Corn, Cotton and Soybean in the United States.
- BIO (2007) Handbook for Understanding and Implementing the Containment Analysis and Critical Control Point Plan for the Production of Plant-Made Pharmaceuticals and Plant-Made Industrial Products.

Usually such activities require a permit that can be obtained after evaluation of a regulatory application. The activities may be subject to conditions that can be part of the law, of the application and/or of the approval. Regulatory compliance indicates that the user observes all the requirements for obtaining the necessary permits as well as all the operational conditions that are imposed on the execution of the intended activity.

While a growing number of countries have a regulatory framework for GMO's, some countries still lack a formal legislative framework. Other legislative frameworks have not reached a sufficient level of operational implementation. In situations where there is an absence of an operational legislative or regulatory system, it is important for FARA, SROs and NARS to decide whether to support transgenic research and collaborations with developers. If a decision is taken to proceed then a research strategy, plan and stewardship programme is recommended to be discussed with the authorities for their input and to seek official endorsement before the start of the project. Information on the intended activities should be of the same quality as would be provided in well established regulatory systems.

Whenever a project or an activity with biological material is envisaged, an analysis can be made of the impact from a regulatory perspective. This analysis is first performed before the onset of a project and is updated at regular intervals or when a change in plans is anticipated. As a project may include different activities in different countries, the analysis may be elaborated in time and include different stages of implementation.

In view of the requirements identified above, the necessary effort is made to ensure that all conditions are met to allow the performance of the intended activities. For the regulatory requirements this includes:

- Analysis of the involved authorities, permits and procedural requirements.
- Planning of the delivery of adequate safety information (possibly relying on third parties).

- Verification of confidentiality treatment and evaluation of proper information to the public.
- Completion of the appropriate files and submission.
- Follow-up with authorities and interactions on open questions.
- Acceptance of approval.
- Analysis of conditions (this is a working document specifying all conditions that are specified in the law, the submission, the approval and any other relevant document).
- Communication of conditions to involved staff and integration in execution.
- Follow-up during execution.
- Reporting to management and authorities as appropriate.
- Conclusion.

It should be noted that certain conditions may be applicable to other parties. For instance during the commercial stage certain conditions on the use and utilization of the crop (*e.g.*, conditions of authorization, monitoring requirements, import/export and phytosanitary requirements) may prevail, which need to be communicated to downstream users and possibly integrated in contractual arrangements.

Two specific cases require additional attention: Product Launch and Product Discontinuation.

Product Launch

Organizations that develop and market biotechnology-derived plant products should consider policies for product launch stewardship as well as appropriate processes and plans that manage the commercialization activities. When carefully thought out, those steps will help an organization initiate actions that promote the responsible introduction of new products and prevent trade disruptions. The results of the planning will facilitate continued global adoption of plant biotechnology-derived products, and bring additional benefits and value to the marketplace.

There are several examples of Product Launch Stewardship documents, but in this training reference is made to the ETS Guide for Product Launch Stewardship[11]

Typically, a Product Launch regulatory strategy is prepared during the Plant Product Development phase and implemented during the Plant/Seed Production phase. It allows a complete overview of permit requirements and management options.
The following activities are foreseen:

- Identification of the person(s) in the organization responsible for product launch stewardship.
- Conduct of a market and trade assessment to identify key import activities prior to commercial launch of any new biotechnology-derived plant product (crop by event) in any country. Factors to consider in conducting a market and trade assessment include:
    - The countries importing the product(s).
    - The types of products (direct product, by-product, processed product) and approximate volume of export to these markets.

11 http://www.excellencethroughstewardship.org/facts/documents/Guide%20for%20Product%20Launch%20Stewardship.pdf

- The regulatory system and how it functions in each country.
- The status of regulatory approval in each country.
- Submissions to appropriate jurisdictions.
- Adherence to international standards, such as the International Plant Protection Convention (IPPC) and the Cartagena Protocol on Biosafety.

- Development of regulatory and commercialization plans to meet applicable regulatory requirements in key production and importing countries (as determined by the market and trade assessment) prior to commercialization of a new biotechnology-derived product.
- Making available a detection method to stakeholders when and where appropriate.

Product Discontinuation

While addressing the Plant/Seed Marketing and Distribution phase, a Product Discontinuation Plan should be developed that addresses regulatory registration strategies, potential impacts on market licensing agreements globally and integrates the needs of stakeholders in the value chain at the moment that the product will no longer be supported.

The objectives of a global product discontinuation are to eliminate product inventories and prevent new market exposure for the discontinued product through company research, development, and/or commercial activities.
Product discontinuation is a process whereby termination of sales of the commercial product is effected and includes the following circumstances:

- Cessation of research and development efforts, if applicable.
- Cessation of commercial seed production, distribution, and sales.
- Elimination of product inventories.
- Termination of licensing agreements.
- Application of appropriate quality-management procedures designed to minimize the presence of the discontinued seed product in other seed products.
- Communication of discontinuation to key stakeholders.
- Varietal de-registration/de-listing, where applicable.

To facilitate product discontinuation, relevant documentation and records should be tracked and archived as appropriate throughout the product life cycle (*i.e.*, molecular characterization, product information, agreements). Throughout the Product Discontinuation phase, appropriate regulatory approvals should be maintained and a developer's internal product-discontinuation process should be properly documented and verified to assist in discussions with regulatory authorities and stakeholders. Product discontinuation should be openly communicated to value chain stakeholders and discontinued product materials (seed, grain, and derived products) generally should be allowed to move through the usual channels for end use and consumption.

Further information can be found in the ETS Guide for Product Discontinuation[12].

12 http://www.excellencethroughstewardship.org/facts/documents/Guide%20for%20Product%20Discontinuation.pdf

2.5. Policies, processes and procedures

In the previous sections concepts like policies, process and procedures have been used to indicate certain components of the Stewardship approach. This section provides a concise review of what they are, how they are determined and some examples. It should be noted again that these are general indications and that the actual situation may differ depending on the typical structure and hierarchy in each organisation.

2.5.1. Policies

A policy is a plan or course of action, as of a government, political party, or business, intended to influence and determine decisions, actions, and other matters. Within the framework of this training document a slightly different definition is preferred namely "**a definite course or method of action selected from among alternatives and in light of given conditions to guide and determine present and future decisions**." This is preferred as it includes clearly the element of selection and guidance.

A policy can be developed by anyone in an organisation; however, as the policy is expected to guide decisions, it needs to be endorsed by top management. A policy that is not fully supported by top management is probably ineffective and will not be adhered to.

Usually a top-down approach is used for developing a policy. Top management sets the overall policy, sub-organisations prepare their own policies in line with these indications for their field of application, which could be geographical or subject related.

Policies can cover virtually any field in the management of an organisation. Some policies are publically communicated as they provide insights in the position of the organisation and can contribute to building public confidence as well as public scrutiny on the actions of the organisation.

A stewardship policy should be appropriate to the nature and scale of the activities of an organisation and is expected to contain the following types of commitments:

- Protecting staff, contractors, visitors, community and environment from potential risks associated with biological material that are developed and used.
- Reducing the potential of unintentional release of biotechnological material.
- Reducing the possibility of unauthorized release of biotechnological material, including the need to conduct risk assessments and implement the required control measures.
- Complying with all legal requirements applicable to products of biotechnology.
- Ensuring that the need for effective biorisk management shall take precedence over all non "health and safety" operational requirements.
- Effectively informing all employees and relevant third parties and communicating individual obligations with regard to handling biotechnology products to those groups.
- Continually improving stewardship performance.

Annex 1 provides a number of examples of policies by companies in relation to stewardship of biotechnology products.

2.5.2. Processes

A process is **a series of actions or operations that results in an end product**. In some cases - especially in manufacturing - it can refer to a continuous operation or treatment. During the complete life cycle of a product very diverse processes will be performed in order to achieve a successful presence in the market.

Processes are typically developed by the functional responsible involved in achieving a certain goal. It may require advanced technical understanding. Processes are normally endorsed by the head of an organisational unit. When working in a formal Good Laboratory Practice organisation, protocols need to be developed in great detail and need to be managed via a separate process.

Experts may be so familiar with their processes, that they omit proper documentation and recording of protocols. Yet such explicit recording is a key part of stewardship as it will allow the identification of Critical Control Points (see section 3.2)

Some examples of processes:

- During Gene Discovery there can be a process to produce genetic constructs. This would involve different steps, ranging from receiving genetic elements, molecular techniques, bacterial cultivation, transfer of plasmids, isolation of DNA, sequencing etc. Together these manipulations lead to the development of a construct. While the process may not be completely identical for two independent constructs, overall the different steps may be very comparable.
- Selecting material for a field trial can constitute a process starting with the identification of the material that is desired, verification of the quality of the material and possible analysis that have been performed, physical preparation of the appropriate quantities of material per plot, labelling of the individual seed bags, preparation of the necessary accompanying documentation and packaging for shipment.

2.5.3. Procedures

Sometimes the term procedure is used to refer to a traditional or established way of doing things. In the context of this training it refers to a particular way of accomplishing something or of acting. In the following section reference will also be made to Standing Operating Procedures (SOP) which are established or prescribed methods to be followed routinely for the performance of designated operations or in designated situations.

Procedures address parts of a process. They tell in greater detail who is expected to do what and in what way in order to achieve a particular result. They can be highly prescriptive and need to be fully adhered to. Deviations should be acted upon.

Depending on the organisation, procedures and in particular SOPs may need to be developed and approved via a specified internal process. Whenever new versions are required the proper process should be repeated.

Some examples:

- A procedure for verification of greenhouse containment features would list who should perform the verification, at what frequency they need to occur, what elements are to be verified and how this should be done, how the results should be scored and recorded.
- A procedure to provide codes that allows unique reference for material and quick tracing of the origin and genetic elements.

- A procedure to react on new scientific findings that could have an impact on the safety assessment of a biotech product.

2.6. Structure and organization

The governance, decision-making rights and individual operational responsibilities for Product Stewardship need to be clearly identified. A multi-disciplinary approach is preferred in order to ensure a close match and harmonisation between stewardship concepts and daily practice.

2.6.1. Internal organization

The exact assignment of tasks may vary depending on the specific structure of each organisation. It is the responsibility of Top Management to determine how these tasks will be taken up and such assignment needs to be properly communicated throughout the entire organisation.

Top Management needs to endorse the general principles of the Product Stewardship approach and as a united team implement stewardship policy. They need to agree on the objectives and identify the necessary resources for fulfilling the stewardship plans. They should review the regular reports on stewardship and in the case of a reported incident ensure full investigation and implementation of the remedial actions required. In addition they have a crucial role in communicating the importance of Product Stewardship throughout the organisation and with third parties.

An organisation can rely on one or more **Stewardship Leaders** (or similar term). These are individuals that have been trained and are mandated by their management to steer the implementation of Product Stewardship in their organisation. As required, they can call upon support and form teams on specific aspects of Stewardship. Their tasks can include:

- Develop proposals on Product Stewardship appropriate for the challenges specific to the organisation.
- Develop methodologies in support of Stewardship tasks (*e.g.* Critical Control Points).
- Guide staff on using such methodologies and to review the outcome.
- Identify training needs and develop training programmes.
- Organize internal audits and/or audits by third parties.
- Accompany the handling of incidents.
- Review any follow-up of audits and/or reported incidents.
- Review other developments and guidance on Stewardship.
- Report to top management on a regular basis.

Organisations are comprised of departments or groups that have a functional line manager or leader who is responsible for daily operations. These **Functional Heads** are key in communication with the involved personnel and in the implementation of the professional working practices. In relation to Stewardship they are expected to:

- Contribute to identifying activities of relevance for Stewardship.
- Critically and creatively evaluate proposals for managing Stewardship in daily situations.
- Communicate and reinforce the importance of Stewardship with his/her group members.

- Report any area that requires further attention and/or is subject for improvement.

2.6.2. Third parties

Stewardship requires **collaborating third** parties to have coherent and robust stewardship processes and procedures in their organisation that meet a similar set of standards. Whenever collaboration includes activities that would be subject to stewardship, the developer should include compliance by the third party as a contractual obligation. It is the responsibility of the third party to adequately cover this request. The developer can offer to provide guidance and references to enable the third party to set up its own Stewardship system for the purpose of the collaboration.

Some aspects will have an impact on other parties and **stakeholders** even if there is no direct relationship. This is for instance the case when preparing for a product launch. Accordingly guidance on product launch Stewardship comprises information for and consultation with stakeholders in the value chain.

3. Introducing stewardship in an organisation

3.1. Development of a Stewardship programme

Before embarking on developing a Stewardship programme it is critical to secure two factors which will largely determine whether the programme is successfully implemented or results in a collection of papers that will contribute little to the performance of the organisation:

- **Support from Top Management** Stewardship can be perceived as an administrative burden. However when properly integrated it enhances efficiency of the organisation, ensures faster access to markets and avoids compliance issues and liabilities. It can be an important asset in public interactions and helps position an organisation as a responsible partner in collaborations. Top Management must be thoroughly convinced of the benefits of Stewardship for their organisation. They should support the programme by establishing the policy, by communicating the importance of Stewardship to the organisation, by assigning proper resources to the Stewardship effort and by engendering a culture of valuing participation and continuous improvement.
- **Buy-in from the Operational Staff** During the development of the programme operations all staff will need to be involved to clarify process and specify procedures. This should guarantee that they are realistic and can be executed. It also supports creating awareness with the people that are on a daily basis involved in the execution of the tasks.

To initiate the development of the programme, it is advisable to get a complete overview of the scope of activities, projects and organisational structure. This will lead to identifying the different phases that are covered as well as the process that are in place.

It will be important to map the objectives that have been determined for each project. For instance it can be questioned if product specification and purity standards have been determined, or if a strategy to produce safety documentation has been established. The different themes offer a reference for this. Whenever a topic has not been addressed it is advisable to discuss with the responsible person what the plans and actions needed are.

Subsequently for each process a critical control point analysis should be performed.

3.2. Critical Control Points

A Critical Control Point (CCP) is defined as **a step at which control can be applied and is essential to prevent, eliminate, or reduce to an acceptable level an activity that may compromise one of the life cycle themes.**
(Note that the term control as used here means "to have/to bring under control," and should not be confused with testing, checking or verification).

The concept of CCP is derived from the 'Hazard Analysis Critical Control Point' (HACCP)[13] concept that was developed in the early 1970s as a system to assure food safety. HACCP is applied throughout the food chain from primary production to consumption of the food product. It is used as a science-based and systematic tool to assess hazards and establish control systems that focus on prevention rather than relying mainly on end-product testing. HACCP is also the tool that the Consultative Group on Agricultural Research ("CGIAR") is advocating to be used within their

[13] CAC. 1997. Hazard Analysis and Critical Control Point (HACCP) System and Guidelines for its Application: Annex to CAC/ RCP 1-1969, Rev.3 (1997). Codex Alimentarius Commission (CACV), Geneva.

International Agricultural Research Centres and by collaborating partners in Africa and across the globe.

In 2003, BIO developed a rigorous set of procedures known as the Containment Analysis and Critical Control Point (CACCP) plan[14]. The CACCP plan was based on best practices as determined through wide experience in manufacturing and industrial processes. Producers used the CACCP procedures to identify potential hazards and apply steps so Plant-made pharmaceuticals (PMPs) and plant-made industrial products (PMIPs) are restricted to the intended use. Confinement procedures were designed to keep these plants controlled and separate to prevent unintended commingling with food and feed crops, the environment, humans, and other non-target organisms.

The ETS Stewardship guides further elaborate on the HACCP approach as a critical element in the identification of CCP where intervention may be required.

According to Codex Alimentarius, the seven principles of HACCP are:

Principle 1: Conduct a hazard analysis
In this preparatory step a complete review is made of the available information and the processes are fully mapped. This includes:

- Defining the scope.
- Describing the product's characteristics, processing and expected use.
- Producing a flow diagram.
- Determination of significant hazards.
- Determination of acceptable levels.
- Consideration of control measures.

Principle 2: Determine Critical Control Points (CCPs)
The analysis should consider the entire process, and ask for each identified hazard, at each step, questions such as:

- Can the hazard be introduced into the product via the raw material under study? If this is the case, is it likely to be at, remain at, or increase to, unacceptable levels?
- Is the composition of the raw material/product critical to the acceptability of the product?
- Does the process under study improve the final product by reducing the hazard to an acceptable level, or by keeping it from increasing to unacceptable levels?
- At this step, can the hazard be introduced into the product from the processing line or the environment, and if so, is it likely to be at, remain at, or increase to, unacceptable levels?

Principle 3: Establish critical limit(s)
The critical limit is the value that separates acceptability from unacceptability for each CCP. They are the maximum values that should never be exceeded. In order to assure this, target values may be established. They take into consideration the variability of control measures. By making these target values more stringent they ensure that critical limits are always met.

Principle 4: Establish a system to monitor control of a CCP
A monitoring system must be established, to ensure that each CCP is always under control, that is, that the critical limits or target values are met.

[14] http://bio.org/foodag/stewardship/pmp_pmip.asp

Monitoring methods should be rapid to be effective. Physical/ chemical tests and observations are preferred, because biological methods tend to be time consuming. Ideally, they should allow adjustments to be made before the situation becomes unacceptable. Full records must be kept of all monitoring data for management, audits, trend analysis and scrutiny by inspectors.

Principle 5: Establish the corrective action to be taken when monitoring indicates that a particular CCP is not under control

When critical limits are not met, the "out of control" situation should be rectified immediately and appropriate follow-up actions taken. Such actions should be planned and described during the HACCP study. Once the cause of the problem has been identified, further corrective actions should be taken to prevent it from happening again.

Monitoring data should be examined systematically to identify the points where controls should be improved or where other modifications are needed. In this way, the system can adapt to changes by constant fine-tuning.

Principle 6: Establish procedures for verification to confirm that the HACCP system is working effectively

Verification is a very important element of HACCP and should always be included. It is intended to provide additional information to reassure the producer (and the inspector) that application of HACCP results in the production of acceptable products.

It comprises two distinct activities, *i.e.*

- demonstrating conformity with the HACCP plan (are we doing what we planned to do?), and
- data gathering (did we meet our objectives, can things be improved?).

It includes activities such as inspections and audits as well as the use of molecular and agronomic tests to confirm that the control measures operate as designed.

Verification is different from monitoring. The gathered data may indicate, for instance, that certain things were overlooked in the HACCP plan or that the monitoring procedure is not good enough to assess the level of control.

Principle 7: Establish documentation concerning all procedures and records appropriate to these principles and their application

Record keeping is an essential element of HACCP. This ensures that information gathered during the installation, modification and operation of the system would be readily accessible to everyone involved in the process as well as to outside auditors.

During the training of stewardship leaders some practical examples of HACCP will be elaborated. A first way of presenting such an analysis is provided in Annex 2.

3.3. Standard Operating Procedures (SOPs)

3.3.1. Establishing, validation & implementation

During the HACCP several procedures will be identified that are essential for achieving the stewardship goals. While most of these may already be in place, some others may need to be introduced. Even for those that are done routinely, many may be part of the daily activity and may not be properly documented. As a consequence the performance of the same procedure by two different people may differ and the performance may change without notice over time. It is therefore important that key procedures are explicitly articulated in written instructions, usually in the form of an SOP.

Before embarking on the individual SOPs an organisation needs to define clearly the people that will be involved in managing the SOPs and the management processes. For instance, it should be clear:

- Who is allowed to make an SOP?
- What is the process of review and approval of an SOP?
- How are SOPs documented and archived?
- What is the mandatory structure of an SOP (see Annex 3)?
- How is staff informed on the latest versions of an SOP
- How is staff trained on a new the SOP?

Whenever an SOP is developed with a certain purpose, *e.g.* as a measure to prevent a certain deviation from the intended goals, then one should consider **validating** that the proposed procedure also is effective to reach that goal. This may not always be possible or some cases may seem too obvious to require validation. In such instances, it may be sufficient to record why no validation has occurred. Validation usually demands a separate effort.

For clarity, the content of an SOP should usually be provided or written by the person who is expert, most familiar and usually operationally routinely conducting the procedure. SOPs require signatures of the person writing the content and be endorsed by their supervisor. Dates are required on the documents, they should be visible to all in the work area (*e.g.* positioned on a wall for regular reference). They should be updated at routine intervals or as improvements are implemented.

The development of an SOP is only the first step. Once the SOP has been accepted, it needs to be communicated to the necessary people and they should be formally trained. This can be done by their immediate supervisor or by any other trainer who has proven to be familiar with the SOP. In some cases training on the applicable SOPs may be a prerequisite before being allowed to perform certain activities. For instance, staff working in field trials may need to be instructed on all applicable measures and conditions before they are allowed to perform field work. Again care will be taken to document that training has happened and it should be verified that the trainees understand the information described in the SOP.

3.3.2. Inventory management

Inventory management has a pivotal role in managing the integrity of biological material. It can be based on a combination of uniform labelling, strict acceptance criteria, review of entry and retrieval procedures to ensure that all material and relevant information is recorded and accounted for.

An organisation needs to define the type of verifications that need to happen upon arrival of material from a different location. This includes verification of the type of material, phytosanitary status, quality and documentation. In some cases it may be necessary to perform molecular tests on biotech trait identity and purity. Additionally it should be confirmed with management, regulatory and legal responsibles that the organisation is allowed to accept the material.

Until the material is cleared the material is kept in a waiting status and no activities can be performed. Upon approval, the material is entered in the inventory and the relevant information is taken up in the information management system.

Throughout the organisation a single labelling system that covers vectors, transforming DNA, host material, transformants & plant material should be used.

There is a direct link with information in central databases and in group-specific databases that allows retrieving information pertinent to the identity of the material. In the event that the material is found to be incorrectly labelled or where correct storage or retrieval cannot be confirmed, the case need to be analyzed and appropriate disposition needs to be determined for the material and any derivatives.

Any intention of retrieval of material from inventory requires internal approval. If the material is retrieved for provision to a third party, then such approval may require the input from management, regulatory and legal responsible.

For each retrieval it will be clear what the intended disposition is. This could be for instance use in an in-house test, transfer to a third party for testing or further development or disposal by inactivation. Depending on the purpose additional testing of identity, purity and/or quality may be required. In such case the disposition of the material cannot occur until the conducted tests are satisfying.

Any retrieval is entered in the information management system including the intended disposition. Disposal as waste will be performed in line with the prescribed regulation and depending on the nature of the material. There should be clear guidelines for sorting and disposition of materials.

3.3.3. Documentation & traceback

Proper documentation is the foundation of any management system. It specifies how the system should work, reflects the implementation of the system in practice and can demonstrate that the system is effective in achieving the objectives.

Management systems rely on good documentation. Although in some cases verbal instructions may be acceptable, in most cases documentation should be available either as hard copies, as electronic copies or as part of information management systems (*e.g.* databases).
Documentation includes (non limitative list providing examples):

- Policy documents, Manuals, SOPs, Work instructions.
- Job descriptions, assignment of responsibility.
- Meeting records, action plans and lists.
- Record keeping for experiments, identity and purity tests, monitoring.
- Databases for results and inventory.
- Reports on safety studies, regulatory analysis, validation, verification, certification.
- Project plans for research and development projects.
- Training plan, training records.
- Audit and inspection reports.
- Incident reporting, incident response.

Traceback is the ability to follow the movement of a biotechnology-derived plant through specified stage(s) of development, production, and distribution of seeds or plants to growers. By the way the inventory databases are designed, this should be possible. Furthermore fast tracing of relationship between different materials should be foreseen.

People entering information have to understand that they are responsible for the quality and correctness. The systems should be designed to reduce the likelihood of human error.

Critical information has to be identified based on different perspectives like scientific value, business interest, regulatory requirements and contractual obligations. The information should be maintained and can be consulted during at least the prescribed period. It is necessary to put security systems in place to prevent a loss of or tampering with information based on a technical failure or malicious intent.

3.4. Infrastructure & equipment

3.4.1. Facilities (Laboratory, Growth Room, Greenhouse, Storage)

An organisation needs to ensure that facilities have proper containment features functioning, that equipment promoting containment is available and that operations are contributing to preventing release of propagatable material.

Based on an analysis of the possible routes for dispersal of viable material, efficient containment infrastructure is selected. In addition regulatory requirements and internationally recognized guidance documents provide indications for suitable containment elements.

As much as possible these elements are incorporated in the design of the facility. In some cases where existing facilities are temporarily used, alternative solutions may be chosen provided they offer a similar level of protection.

Some facility features require regular verification of their performance status. *E.g.* ambient factors that could influence the quality of material and containment have to be monitored. Routine internal inspections of the facility must be undertaken to confirm that the appropriate level of containment is maintained.

The facilities are equipped with state-of-the-art equipment that guarantees high quality research and protection of the operator and the environment. Typical laboratory and growth room equipment (*e.g.* biosafety cabinets, autoclaves, ultra-cold storage, use of cross-pollination preventing bags) should be specifically chosen for the activity and be regularly verified. Other activities may require other equipment like seed cleaners, seed counters, etc. When possible these should be dedicated or clear SOPs should be available to describe how to clean them between handling two different materials. Personal Protective Equipment, intended to protect staff and to prevent dispersal of material should receive special attention.

Professional operations by trained staff are crucial for ensuring the daily achievement of the Stewardship goals. Care should be taken to integrate stewardship aspects into the normal daily activities and be routine so that attending to stewardship guidelines does not lead to extra work and that there is less risk that they are left out. Some examples:

- Labelling of materials.
- Ensuring reproductive isolation within the facility.
- Space assignment within the facility.
- Equipment cleaning prior and after use.
- Appropriate disposition of plant material.
- Information entry in a unified system.

3.4.2. Field operations

Deployment of regulated Genetically Modified crops in the field must be confined to reduce the potential for exposure and of dispersal in space and in time of propagatable material.

Field locations have to be carefully chosen along pre-defined criteria. Depending on the case such criteria might include the geographical location of the site, climatologic and geological factors, the likelihood and proximity for cultivation of a compatible crop in the expected timeframe of the trial, the proximity of protected areas and areas with a high conservation value, the history of cropping and treatment with plant protection products.

For the conduct of field trials, breeding equipment (*e.g.* small precision seeding machines, precision harvesters) may be used. These are usually equipped to handle very small quantities of material with high precision. They can also be thoroughly cleaned before changing between materials. In later stages also larger equipment may be required. The harvested material is usually treated with seed cleaners, sorters, counters, etc,.

Irrespective of the long standing breeder's experience, an analysis has to be made on how this equipment can be optimally used and if the manipulations could introduce risks for any of the Stewardship themes.

It should be clearly defined who is allowed to operate in field trials, what training is required what other activities they can perform under what conditions. For instance, it may be requested that people who contribute to a field trail with a biotechnology product, need to change clothes before working on other non-biotechnology material.

Adequate field operations are essential. They have to be elaborated and include:

- Labelling of materials.
- Establishment and verification of reproductive isolation measures around the field trial site.
- Verification of reproductive isolation within the field trial site if required for transgenic purity.
- Equipment cleaning prior to leaving the trial site and sometimes between different seed batches.
- Appropriate disposition of plant material after harvest.
- Post-harvest land use restrictions.

Most regulated field trials are subject to in-trial and post-trial monitoring. An official report to the authorities may be required.

3.5. Internal implementation

The previous parts in this section provide a general overview of how the Stewardship management system can be elaborated. As pointed out before, the actual plan will largely depend on the organisation and the specific activities. For instance an organisation that is only advancing to Gene Discovery may have limited interest in developing an approach for advanced planning of regulatory studies and Product Launch Stewardship. Others may not be involved with Gene Discovery but may integrate transformation events selected elsewhere and bring them forward via local testing and classical breeding. In this case, all phases starting with Plant Product Development may need to be considered. It is therefore essential to start the implementation with a good understanding of the activities and ambitions of the organisation.

Stewardship is overarching as it touches upon many themes that are central to bringing a biotech product though its life cycle. As a consequence it is a very demanding and encompassing effort, which will require involvement of virtually

everyone in the organisation. Creating awareness and inviting collaboration are very important to progress.

Many organisations already have established routines and procedures. People may have been trained on specific elements *e.g.* field trial compliance. The Stewardship project can benefit from these and merely upgrade the existing systems in a step-wise way. In fact it may be more straightforward an efficient to integrate Stewardship into existing processes and procedures, rather than establishing a completely new system in parallel.

Introduction and consolidation of Stewardship, in line with the concept of continuous improvement, can occur in a stepwise fashion. The Stewardship Leader needs to establish an action plan and give priority to those areas where gaps exist or further improvements are urgently needed. This way also guarantees that Stewardship is not considered an unnecessary burden but on the contrary demonstrates that it is a way to enhance the performance of the organisation as a responsible developer and user of biotechnology.

4. Incident response

Incidents can occur at any stage of the product life cycle. Therefore, an organization should have systems, processes, procedures, and resources in place to respond to potential incidents involving biotechnology-derived plant products across the life cycle.

Incidents should be dealt with quickly and effectively to minimize impact on the organization and its stakeholders. Preparedness followed by directed and effective response is important to successful incident response, together with the implementation of corrective and/or preventative actions that can help reduce the likelihood of a reoccurrence. Prompt and thoughtful response actions will help to maintain strong stakeholder relations.

4.1. What is considered an "incident" in this context?

In general terms, "incident" refers to **an occurrence of an action or situation that is not according to the desired course** and that has/could have important consequences on realizing the objectives. In the case of stewardship the objectives are captured in the themes discussed before.

In stewardship it is preferred to refer to "incident" rather than "accident" or "emergency", as these terms suggest respectively loss or injury and an exceptional state that calls for immediate action.

Examples of potential incidents that may occur throughout the product life cycle could include:

- Unintended/unauthorized release of propagative plants into the environment;
- Unexpected/unauthorized third-party intervention;
- Product non-conformance;
- Detected levels of biological traits at unapproved levels;
- Unexpected research study findings;
- Non-compliance with laws and/or permits; and
- Significant seed-quality failure.

4.2. The Incident-Response System

An organization should have an incident-response system in place that is tailored to its type and scope of operations and activities. This could include having:

- Defined roles and accountabilities for incident response, including response team leadership and subject-matter experts in regulatory, legal, compliance, commercial, research, supply chain, and communications;
- Defined process flow diagram for incident response;
- Defined escalation process including response triggers that define appropriate reactions to specified types of incidents;
- Established communication networks for dissemination of information internally and externally;
- Defined stakeholder maps to facilitate timely inclusion of key parties;
- Defined documentation requirements, as appropriate and as determined by legal counsel, and

- Established ongoing training program to embed the defined incident response system, processes and procedures into the organization.

Advance planning and preparation is important to the successful resolution of an incident. In the design, development, and implementation of incident-response processes and procedures, an organization should take into account the variety of activities and types of potential incidents that may occur.

4.3. Incident-Response Process

The following lists the steps of a typical incident-response process.

Step 1 - Notification of potential incident

The person who initially identifies or suspects a potential incident quickly outlines the circumstances so that it can be promulgated to appropriate experts and managers within the organization; and then managed according to the subsequent steps in the process. A basic potential incident-response form should be available to collect information as appropriate, and can include:

- Description of incident;
- Time, date, and place of incident;
- Involved personnel;
- Promulgation process for information (at the local and/or global level);
- Events leading up to incident;
- Any associated factors or circumstances;
- Potential indirect effects (*e.g.*, health, safety, environment);
- Actions taken, proposed next steps; and
- Name of personnel receiving report.

This preliminary report is important to the successful management of the incident. It may initially be a verbal report, but it rapidly should become a record-and-communication document according to organization guidelines.

Potential incidents may also be identified by external sources (*e.g.*, auditors, consultants, co-operators). As feasible, there should be response procedures established with these external sources for prompt notification of an incident to the organization.

Step 2 - Verification of incident

Initial notification of a potential incident should be communicated to the appropriate internal contact(s) (*e.g.*, stewardship, regulatory, quality, compliance, and/or legal), who should confirm whether there has been an incident and its nature (*e.g.*, unauthorized release, product non-conformance, vandalism, natural disruption, etc.).

At this point, it is important to confirm that there has been no mistaken identification and that an incident involving the organization's product has truly been verified as indicated.

Step 3 - Scope the incident

A small team of experts should rapidly scope out the potential impact and magnitude of the incident. In addition to physical consequences, the potential regulatory implications, regulatory obligations, and liability/litigation risks should be evaluated by reviewing the appropriate documents, such as government regulations, permit conditions, contracts, and legal agreements.

The initial scoping exercise needs to be fast and extensive so that the appropriate internal and external response mechanisms can be initiated with appropriate information communicated to key stakeholders.

This initial scoping exercise should comprise the following details:

- Clear definition of the incident;
- Initial quantification;
- Definition of potential impacts;
- Identification of potential legal requirements (*e.g.*, reporting obligations);
- Scenario analysis of actions and consequences;
- Identification of stakeholder (*e.g.*, regulators, customers, grain trade, food chain, etc.); and
- Review of relevant agreements and potential insurance coverage under applicable policies.

Step 4 - Convene Incident Response Team

The **response-team structure** and membership will depend upon the initial assessment of the scope, the potential impact of the incident, and the expertise needed to manage the situation.

The **response team leader** should have the expertise, time, and resources to manage the issue in an expedient manner. It is important to have clarity on roles and responsibilities, as well as transparency and coordination across sub-teams. Sub-teams, with local or global focus, may also be needed for major incidents so that specific stakeholder needs are covered (*e.g.*, government staff, industry trade partners, distributors, local or international media).

Step 5 - Develop and implement the Incident Response Plan

Clear analysis combined with timely and effective response can lead to successful handling of an incident. A dedicated response team should focus on resolving the incident.

Response activities should consider the framework of stakeholder commitments, regulatory requirements, contractual obligations, and other legal requirements that may include confidentiality responsibilities. Efforts should be undertaken to maintain customer, trade, and public confidence.

Members of the incident-response team should develop a response plan and implement remedial actions. The response plan should identify the actions to be taken, the persons accountable for the actions, and when the actions should be completed. The response plan will need continuous updating as new facts emerge and should be transparent as a working tool to all team members.

Stakeholders should be identified and appropriately informed of an incident and any potential impacts on them. Communications should take place within the relevant regulatory and legal framework. Incoming questions should be adequately addressed by informed expert staff.

Step 6 - Process improvement

Even when an incident has been handled successfully, 3 types of follow up are recommended as part of continuous improvement of the organisation:

- Review the effectiveness of the corrective actions after an appropriate time.

- At an appropriate phase in managing the incident, conduct an internal investigation and recommend process improvements that could be made to help reduce the likelihood of similar future incidents.
- Review of the organization's incident response process and procedures should also occur in a timely manner following an incident.

Any necessary process improvements and training should be implemented to correct identified deficiencies.

5. Training & communication

In this section training and communication will be addressed jointly. Although there are differences, similarities in approach allow this combination. Therefore wherever "communication" is mentioned, it would be possible to replace it with "training".

5.1. Developing a communication plan

Having a communication plan in place is an essential component for good project management. This communication plan ensures that all stakeholders are equally informed of how, when, and why communication will happen. Communication is often a very effective way to solve problems, deal with risks, and ensure that tasks are completed on time. Successful communication plans will identify stakeholders, the information to be communicated, and how this information will be communicated. It should not leave anything to chance.

As pointed out before, stewardship requires a structured approach to training of all staff involved. Also communication with different stakeholders has been mentioned several times. Yet, it has to be recognised that communication and training is relevant at very different levels. Here are some examples:

- In an organisation, it will be important to create awareness for stewardship and the importance of individual contributions to the over-arching objectives;
- When SOPs are implemented or modified, the involved staff needs to be informed and trained. Records of such training need to be maintained;
- A specific set of information may be required for visitors to a facility as a prerequisite for being allowed access;
- Briefing media on a field trial application will require well balanced messages, adapted for understanding by non-technical public;
- Communication of incidents will need special care to ensure that the organisation is seen as responsible.

Stewardship requires that training and communication occurs in an organised and planned way. There are no preset indications on transparency or obligations to share information beyond what would be required for achieving the stewardship objectives. *E.g.*, Product Launch Stewardship explicitly requires communication with stakeholders down the product chain before launch of the product. Other information may be required to become publicly available due to regulatory requirements. Beyond these obligations, each organisation has the freedom to decide which information to share or to keep confidential. Stewardship only requires an organisation to consider how this information shall be handled ideally in advance of the request.

5.2. Responsibilities

As in other sections of this document, it is also important that roles and accountabilities are well defined in advance. There are different roles to consider:

- **Communication plan manager** It is advisable that one person maintains the communication plan and monitors progress. As there will be different elements to communicate and provide training on, there may be different plans and different managers. They can combine this role with one of the subsequent responsibilities.
- **Communication content** It should be clear who (individual or group) decides on and formulates the content of the communication. A broader group can provide input, but it must be clear what the agreed messages are. For more

complex issues, it would be appropriate to identify a multi-disciplinary team, possibly including representatives from other parties.

- **Communicator** This will be the individual or group of people selected to convey the messages. In case of training, it will be the trainer(s). For external communications, it would be the assigned spokesperson of the organisation. On other subjects, a broad group of communicators may be involved, but as a prerequisite they should all have received sufficient information and training to fulfil this task. Along the same lines, it is important that an organisation establishes a system to transfers inquiries, *e.g.* by third parties such as media, to the assigned spokesperson.

5.3. Formulating messages

An essential part of preparing for communication is formulating of key messages. Key messages on stewardship include:

- Stewardship is the responsible management of a biotech product from its inception through to its use until its discontinuation.
- Stewardship is a process of continuous improvement.
- Stewardship reaches beyond regulatory compliance and involves all stakeholders involved in the product life cycle.
- Stewardship helps to realise the benefits of biotechnology by supporting the delivery of safe, approved products of a high quality and purity.

Clearly, when other aspects are targeted, appropriate messages should be formulated. *E.g.*, when preparing for a field trial, it would be appropriate to foresee a selection of messages that will relevant for that trial, for the regulatory requirements, etc.

The way these messages are articulated will largely depend on the tools that will be chosen for the communication. A few examples include integration in training materials, indication as a subject of a press release or part of a Question & Answers document.

5.4. Identifying the target group

5.4.1. Internal

The main objective is the creation of awareness, soliciting of commitment and training of the internal organisation. It will largely determine if stewardship is successfully implemented or not. Without this proper implementation, external communication will not be carrying great weight and can even be counterproductive.

Stewardship requires buy-in at different levels and this can be achieved by involving staff in the analysis of CCP and establishment of procedures. Also trainings can be carried out at a suitable operational level making the direct link to the actual situation. Identifying the target group in this case will require that a training plan is in place that clearly specifies who is expected to follow which training.

5.4.2. Third parties and stakeholders

Communication with project partners and other stakeholders in the product lifecycle is an important element of stewardship. In principle there is a clear common goal, *i.e.* bringing improved agricultural products to the market. Nevertheless, one needs to take into account that the interests of stakeholders may differ significantly. *E.g.*, a trade organisation may be primarily concerned with securing international markets. This requires that before communication these interests are well understood or at

least that during communication sufficient openness is maintained to appreciate the motivation of the other parties.

5.4.3. NGO's, media and public

There may be occasions where a broader communication is required. In such case it can no longer be assumed that these organisations share the viewpoints and objectives of the organisation. In fact, they may be suspicious and may have concerns over the use of biotechnology.

Communication on biotechnology sometimes escalates in a debate of opposing views. This creates confusion and leaves the public without reliable reference. From a stewardship perspective, it can be indicated that developers need to provide clear, reliable, factual information. While clearly motivated to realise the benefits of biotechnology, it is important to understand that there may be diverging views. Allegations that are scientifically unfounded can be addressed without getting distracted from the main message of responsible use of a very promising technology.

Stewardship is another element to show that biotech developers are aware of the concerns and install process to address potential issues. Within the concept of continuous improvement, this approach is not static and will continue to be adapted as new insights are discovered. While addressing these, the developers can bring in full confidence products to the market that allow improved livelihoods of the farming community.

5.5. Choosing tools

Depending on the audience and communication goal, specific communication tools may be chosen. Here are a few examples:

- A formal hands-on training session with a trainer and trainee(s);
- An SOP, that the trainee has to read and sign for acceptance;
- Mentioning the Stewardship policy on the organisation's website;
- A section in an organisation newsletter reporting on the implementation of Stewardship;
- A written instruction for a visitor to a field trial site;
- A town-hall meeting with farmers planting fields close to a field trial
- A press-release;
- A press-conference or interview.

It is likely that some approaches may be selected on the initiative of another party. *E.g.*, the press may call for an interview although this was not planned in the communication plan. It is important that an organisation decides in advance on how to handle such requests in order not to be dragged into an undesirable situation. Communicators that will use communication tools must have received proper training in handling the tool. This is too often underestimated.

5.6. Monitoring effectiveness

Given that communication fits in a communication plan, it will be essential to monitor the effectiveness of the communication. Like any other project activity, it will be important to establish if the goal has been reached. When addressing stewardship, the level of understanding and the awareness can be tested by questioning staff. For SOPs, it would be possible to check if they are understood and applied correctly. In a broader communication, it may be of interest to monitor how other stakeholders react or how the information is reported. Depending on the outcome, the communication plan or approach may need to be adapted.

6. Verification & audits

During implementation and operation of a management system, regular checks must be included. This is also essential in any system that aims for continuous improvement. In this section different types of checks are presented as well as recommendations on how to structure such an effort.

6.1. Types of verification

6.1.1. Process, CACCP and validation

As pointed out before, clearly mapping the involved processes is the first step. The process will be designed in such a way that the chance for an unwanted event to occur will be limited and that controls may be exerted. In order to guarantee that the methods contribute effectively to the intended goal, formal validation may be required. **Validation means the process of confirming that something (an application, an experiment, a piece of equipment, etc) consistently fulfils the requirements for a specific use.**

Example: The CACCP analysis identifies that plant material produced in the lab needs to be destroyed before disposal. The organization has access to an autoclave which has been used for inactivation and intends to use a standard protocol (duration, temperature, pressure). Validation could consist of determining that after treatment of a typical batch of plant material no viable plant material can be found.

Typically validation is done only once and before the actual use. Validation should be repeated whenever a change in the process or equipment is envisaged (e.g. changing the pressure settings).

Validation should be properly documented.

6.1.2. Monitoring control functions

CACCP also highlighted the importance of monitoring control functions. These should allow adjustments to be made before the situation becomes unacceptable. Some pieces of equipment allow permanent registration of control functions, whereas others may only indicate extreme values. They should reflect the critical limits determined in the CACCP analysis.

Example: In the case of destruction by autoclaving, it may be critical to ensure that a certain temperature has been maintained during a certain period. Some machines are equipped for registering the evolution of temperature and the record can serve to control that the process has run adequately. If the process didn't run as planned, then the possible impact on inactivation as well as the cause for the deviation needs to be evaluated.

Full records must be kept of all monitoring data for management, audits, trend analysis and scrutiny by inspectors.

6.1.3. Verification

Verification aims to establish the correctness of a theory, fact, etc. In this context, verification is the activity to establish that by implementing the actions required in the CACCP plan (are we doing what we planned to do?) the intended quality, purity, safety, containment and compliance are met (did we meet our objectives? can things be improved?).

Verification is a very important element of CACCP and should always be included. It may help to identify areas for further improvement.

Example: When verifying the autoclaved material reveals viable structures, it may mean that the autoclaving procedure may not be adequate for that type of material although applied correctly according to the designed process. Further investigation should reveal why this is the case and how the process can be adapted to make it effective.

6.1.4. Audit

The general definition of an audit is a methodical examination and review of a person, organization, system, process, enterprise, project or product. In this context, the term audit refers to **a systematic effort to verify the implementation of a stewardship management system.** Like for quality audits, this is usually performed in preparation of certification.

Audits are essential to verify the existence of objective evidence of processes, to assess how successfully processes have been implemented, for judging the effectiveness of achieving any defined target levels, providing evidence concerning reduction and elimination of problem areas and are a hands-on management tool for achieving continual improvement in an organization.

To benefit the organization, quality auditing should not only report non-conformances and corrective actions but also highlight areas of good practice. In this way, other departments may share information and amend their working practices as a result, also enhancing continual improvement. It should not be perceived as a repressive system, rather as a means to excel.

Typically an audit is conducted by an independent party. This doesn't mean that it is obligatory a party from outside the organisation. *E.g.* it would be possible to have people from different departments or from different institutes performing audits with colleagues. Similarly, organisations that have their own internal quality and safety, health and environment structures may have dedicated people to perform internal audits. Nevertheless, in many cases audits will be performed by external specialists that have received specific training and that work according to recognized standards. *E.g.* the ETS programme has trained auditors to perform third party audits which are required for ETS members.

Some organisations also implement "Self-audit"" as a tool for staff to broadly evaluate specific objectives in their area. It is typically structured as a checklist or cascade of questions that directs a systematic review of all important aspects. Self-audits rely on the honesty and seriousness of the individuals answering the checklist. They should be verified occasionally and individuals should be able to consult someone when in doubt. The person completing the self-audit should be knowledgeable about the operations of the particular area and have the authority to effect positive changes, if needed. Appropriate persons to complete the self-audit may include the PI, supervisor, lab, or department manager, designated staff member, or a safety committee representative.

6.1.5. Inspection

Although the term "inspection" can have different meanings, it is more commonly used to refer to **verifications made by officials**. The main objective in this case will be to verify if the activities are performed in compliance with the legal conditions.

As stewardship programmes include the goal of complete compliance with all legal requirements, inspections are an important element. An organization will therefore cooperate with inspectors and make sure that any indication is properly documented and addressed.

6.2. Audit process

6.2.1. Audit Preparation

It is important that both the auditor and the auditee have a common understanding of the audit process. They must jointly determine the specific scope and objectives of the audit. The auditor prepares an audit plan that should be accepted by the auditee before the on-site audit activities begin. The plan should confirm audit objectives, audit criteria and any reference documents, audit scope, dates, places and timing of on-site audit activities, working and reporting language, logistical arrangements, confidentiality and audit follow-up actions.

The auditor and auditee should specify document confidentiality, retention and destruction requirements in the formal agreements between these parties. The auditor should review, handle and retain auditee documents exclusively and in strict accordance with those agreements.

6.2.2. Performing the audit

The audit typically starts with an opening meeting to confirm the audit plan, scope and timeline. It is also an opportunity to summarize how the audit activities will be undertaken and for the auditee to provide relevant site and/or organizational overviews.

During the audit, information relevant to the audit objectives, scope and criteria is collected by appropriate sampling and is be verified. Audit evidence is evaluated to determine whether quality management systems are in place. The determination is summarized by the auditor to indicate locations, functions or processes that were audited.

At the closing meeting the audit findings and conclusions are presented so that they are understood and acknowledged by the auditee. Any differences of opinion regarding the audit findings and/or conclusions between the auditor and the auditee are discussed and, if possible, resolved during the closing meeting. In the closing meeting, the auditee has the opportunity to ask for clarification around audit findings and to respond with additional objective evidence as appropriate.

6.2.3. Audit Report

Some programmes have very specific reporting requirements. *E.g.* ETS requires that an Excellence Through Stewardship™ Summary Audit Report is submitted by the auditor to the Excellence Through Stewardship™ Executive Director.

Notwithstanding such specific requirement, the auditee may wish to receive a more substantial report indicating all the findings in detail. The auditee will then evaluate the findings and document resulting actions.

7. References

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- Biotechnology Industry Organization (2007). Confined Field Trials of Regulated Genetically Engineered Corn, Cotton and Soybean in the United States.
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8. Glossary

Many of the definitions used in this glossary have been taken over from Excellence Through Stewardship™ Guides. Readers are referred to the original documents for further specifications

Adventitious presence (also known as low-level presence, or LLP): Refers to the unintentional and incidental commingling of trace amounts of one type of seed, grain or food product with another. Adventitious presence (AP) is an unavoidable reality of plant biology, seed production and the distribution of commodity crops. While adventitious presence can be minimized, as a practical matter it cannot be eliminated entirely and is not unique to crops enhanced through biotechnology. Adventitious presence of biotech products does not necessarily compromise food safety.

Containment Analysis and Critical Control Point (CACCP) plan: A rigorous industry protocol to enhance compliance with federal regulations in two key product categories: Plant-Made Pharmaceuticals (PMPs), in which proteins produced in plants are used in medicines; and Plant-Made Industrial Products (PMIPs), in which plant proteins are used in industrial products. The CACCP plan is based on best practices and is endorsed by numerous U.S. government agencies and industry associations. CACCP protocols identify potential hazards and control points, and outline management plans to ensure proper handling.

Event (also known as biotech event or transformation event): The result of a specific and unique procedure during which a gene that enables desired characteristics is inserted into the genome of a plant.

Gene: The fundamental physical and functional unit of heredity. A gene is typically a sequence of DNA that encodes a specific functional product (such as a protein or RNA molecule).

Genetically modified organism: Different legal frameworks offer slightly diverging definitions of what is considered a genetically modified organism (GMO). Developers are advised to confirm the exact status of their products. In the most commonly used terminology, GMO refers to an organism in which specific genes or DNA sequences have intentionally been introduced, deleted, or rearranged using the methods of modern molecular biology, particularly those referred to as recombinant DNA techniques.

Herbicide-tolerant crops: Crops that have been developed to survive application(s) of particular herbicides by the incorporation of certain gene(s) either through genetic engineering or traditional breeding methods. The genes enable crops to survive the application of certain herbicides to provide effective weed control without damaging the crop itself.

Insect Resistance Management (IRM): A set of strategies designed to reduce the frequency and slow the evolution of resistance to control measures by insect pests. Unlike with any other crops, growers of insect protected biotech crops have from their first plantings used a variety of resistance management measures. These have included the widespread use of refugia - the setting aside of a certain area of untreated crops to provide a haven for insect pests to reduce the pressure on them to adapt to the control measures employed.

Introgression: The common phenomenon in which genes move from one population to another, usually via pollen carried by wind, or animal pollinators such as birds or insects.

Stewardship: Product stewardship is the responsible management of a product from its inception through to its ultimate end and discontinuation. In agricultural biotechnology, stewardship includes careful attention to the safety of products and their market impact is essential for high value products in any industry.

Traceback: the ability to follow the movement of a biotechnology-derived plant through specified stage(s) of development, production, and distribution to growers.

Transgenic: An organism that has had genes from another organism added to its genome through recombinant DNA techniques.

Annex 1: Examples of stewardship policies for biotechnology products.

Bayer Cropscience

http://www.sustainability2008.bayer.com/en/product-stewardship.aspx

Safety is our top priority in the development and use of biotechnology. Bayer respects consumers' rights to receive information and freely select food products, and observes all relevant legal provisions. We have spelled this out in our Position on the Responsible Use of Gene Technology and in specific directives in the subgroups and service companies. Before a new product is introduced to the market, it is subjected to a stringent registration processes to determine whether it is safe for people, animals and the environment. We understand the concerns about genetically modified organisms (GMOS) expressed by society, but we are convinced that GMOS do not represent a safety risk when the legal requirements and corresponding safety checks are observed.

Dow AgroSciences

http://www.dowagro.com/pgb/commitment/product/
Product Stewardship

Product stewardship is the responsible and ethical management of a biotechnology product from its discovery or development through to its ultimate use. From discovery and development of a product to its delivery and use in the market, Dow AgroSciences ensures good stewardship practices are in place every step of the way.

Before a biotech product can be field-tested or introduced into the market, approvals by appropriate governmental agencies are required. Using the criteria established by these agencies, Dow AgroSciences conducts extensive, validated tests for our biotech products. All research is conducted in strict compliance with applicable laws and regulations. For more information on field research trial compliance, please visit: Field Research Trial Compliance.

In addition, Dow AgroSciences' corporate policy requires that we apply a comprehensive Risk Review Process at key stages of a product's life cycle. This process begins at discovery and development, and continues through production and post marketing. As part of our commitment to Responsible Care, health and safety information on our products is made available at the following website: http://www.dow.com/productsafety/. For peer-reviewed, published studies on the benefits and safety of biotechnology, visit CropLife International's database at: http://croplife.intraspin.com/BioTech/.

Dow AgroSciences is committed to bringing new biotechnology products to the marketplace in a responsible manner. As a member of both the Biotechnology Industry Organization (BIO) and CropLife International (CLI), Dow AgroSciences supports BIO's Product Launch Stewardship Policy and CLI's Product Launch Stewardship Guidance.

Dow AgroSciences, through our affiliates and licensees, takes great efforts to make sure that our customers understand the stewardship obligations for our products. Our product stewardship plans are based on grower and grain channel education, reinforcement through written and verbal communications, including product use

guides, and grower assessments. Click on the following links for more information on Insect Resistance Management, Grain Marketing.

Dow AgroSciences participates in business organizations and associations globally to promote the safe research and development, production, distribution, and use of biotechnology products. Dow AgroSciences supports the implementation of stewardship best practices as broadly as possible throughout the industry and value chain.

Monsanto

http://www.monsanto.com/responsibility/stewardship.asp

Various Monsanto teams focus on product stewardship from lab to field: financial stewardship to ensure that financial standards are met; environmental, safety and health stewardship to protect the safety of our people, communities and the environment; and societal engagement to consider whether we are doing the right things and doing them right.

Stewardship and The Pledge: Meeting Monsanto's high stewardship standards, and operating with integrity in accordance with our Pledge values.

Product Stewardship Safety: The legal, ethical and moral obligations to ensure our products and technologies are safe and environmentally responsible.

Stewardship Information for Growers: Insect Resistance Management (IRM) guide, Technology Use Guide (TUG) and educational materials for U.S. growers.

Monsanto's Glyphosate Endangered Species Initiative: Monsanto is committed to sustainable agriculture and rigorous product stewardship. As leaders in the stewardship of Roundup agricultural herbicides, we are implementing a new stewardship program called the Glyphosate Endangered Species Initiative. This initiative depends on Monsanto working in partnership with growers and applicators.

BIO Product Launch Stewardship Policy and Self-certification Letter: Monsanto's commitment to implementing the "Excellence through Stewardship" program and Product Launch Stewardship Policy.

Seed Patent Protection: Patents, like copyrights, are a form of intellectual property protection that legally prohibits unauthorized duplication of a product. In agriculture plant varieties and seeds with enhanced biotech traits may be patent protected whether soybean, strawberries, flowers etc. Monsanto is one of many seed companies that patent their innovations. Monsanto's primary reason for enforcing its patents is to ensure a level playing field for the vast majority of honest farmers who abide by their agreements, and to discourage using unpaid technology to gain an unfair advantage.

Syngenta

http://www.syngentabiotech.com/biomain.aspx

Syngenta designs and develops products to improve agriculture and bring benefits to rural communities. The company is committed to implementing high standards of stewardship for the safe, effective and environmentally responsible production and use of its products.

http://www.syngentabiotech.com/biopolicy.aspx

BIO PRODUCT LAUNCH POLICY

SYNGENTA IMPLEMENTATION PRINCIPLES

Syngenta is committed to bringing new technology to the market place to help meet the growing demand for food, feed and fuel. In doing so, Syngenta supports the BIO product launch policy which was developed by the members of BIO's Food and Agriculture Section. We will be guided by the following principles as we commercialize new products:

1. We will conduct market and trade assessments to identify key import markets for all of our biotech products prior to product commercialization.

2. For each biotech product, at the time U.S. submissions are completed, we will begin to consult with the major, relevant trade and value chain stakeholders on our detailed plans for pre-commercial activities, and full scale commercialization.

3. We will meet all necessary regulatory requirements in key exporting countries (where the seed will be commercialized) and importing countries that have functioning regulatory systems, which currently include the United States, Canada and Japan, prior to commercialization, unless determined otherwise in consultation with the value chain that a dedicated grain management system is workable for a specific product.

4. We will make available prior to commercialization a reliable detection method or test that enables event identity in the crop.

5. We are committed to the principles of good stewardship, which are exemplified through the responsible management of our products across their lifecycle, from research through development and commercialization to their discontinuation and withdrawal from the market.

6. We will continue to work at the global level with the value chain to engage in efforts to harmonize science-based agriculture biotechnology regulatory approaches to achieve Global AP tolerances and synchronous authorizations.

Annex 2: Example of an HACCP

Note that these are selected and fictitious entries. They are not intended to cover the entire process, but only serve as example)

Activity	**Construct Design**				**Version**	1.0
Location					**Date**	
Module	X	**Contained Laboratory**		**Confined Field Trial**	**Author(s)**	
		Contained Growthroom		**Plant & Seed Production**	**Reviewed and approved by (name/date)**	
		Contained Greenhouse		**Commercial Production**		

1. Raw Materials

Description	**Risk**	**CCP**			**Measure**	**Monitoring**	**Corrective Actions**
		Point or Process	**Parameter(s)**	**Critical limits**			
Synthetic nucleic acid material	Wrong nucleic acid material	Receipt of material	GOI (Gene of Interest)	To be determined in function of what is to be received by contract	- Upon receipt, confirm coherence accompanying documentation (certificate) with expectation	- External sequence check of material	- Decide on disposal or allowed use of material - Inform sender of material
Vector	Misidentification and/or mislabelling	Entry in and retrieval from vector storage	Presence of building blocks in the vector	Presence of intended building blocks / absence of any unintended building blocks	- Unique labelling of vectors - Verification of label and information upon entry	- Verification building blocks through sequencing (digest)	Decide on disposal of vector
Agrobacterium tumefaciens strains	Misidentification and/or mislabelling	Entry in *Agrobacterium* storage	*A. tumefaciens* cells	To be determined in function of desired *Agrobacterium* strain	- Verification of label of *Agrobacterium* upon entry and retrieval in -80 °C storage	- Analysis transformation results	Decide on disposal of *Agrobacterium*

2. Processes							
Description	**Risk**	**CCP**			**Measure**	**Monitoring**	**Corrective Actions**
		Point or process	**Parameter(s)**	**Critical limits**			
Set-up of experiment	Produced events present regulatory hurdles	Decision on using plasmid construct as contained in *Agrobacterium*	Presence of Antibiotic Resistance Marker (ARM)	Presence of intended ARM/ absence of any unintended ARM in designed plasmid for transformation	Internal procedure for creation of specific event	- Analysis of transformation results - Verification inserted genetic elements of *in vitro* plants	Decide on disposal of material
Design synthetic gene construct	Error in design/gene sequence	Before and at the moment of sending out sequence for synthesis	GOI	Nucleic acid sequence (internally known as '*in silico* construct')	Internal procedure for creation of specific event	Sequence check by third person/project team	Redesign gene construct
Transformation of plasmid construct containing the expression cassette in *Agrobacterium*	Mix-up between different plasmid constructs / Misidentification	Retrieval from vector plasmid storage for electroporation	Presence of correct plasmid construct in *Agrobacterium*	Presence of intended genetic elements/ absence of any unintended genetic elements	- Unique labelling of plasmid constructs and transformed *Agrobacteria* - Verification of label information on plasmid constructs upon retrieval - Use of selectable markers on transformed *Agrobacterium* cells - Entry of required information in database	Analysis of transformed *Agrobacterium* through re-transformation in E. coli to verify inserted genetic elements of plasmid construct	Decide on disposal of *Agrobacterium* and/or plasmid construct

3. Products							
Description	**Risk**	**CCP**			**Measure**	**Monitoring**	**Corrective Actions**
		Point or process	**Parameter(s)**	**Critical limits**			
Agrobacterium tumefaciens with plasmid containing the expression cassette	Misidentification and/or mislabelling	Entry in bacterial stock (storage)	Presence of genetic elements	Presence of intended genetic elements/ absence of any unintended genetic elements	- Unique labelling of transformed *Agrobacterium* cells - Entry information on transformed *Agrobacterium* cells in database upon putting these in storage for further use	Verification inserted genetic elements of *in vitro* plants	Decide on disposal of transformants

Annex 3: Example of typical components of an SOP

It is expected that the SOPs of an organisation conform to specific criteria on format and content. Therefore, it is advisable to develop a template and instructions on how these should be managed. Furthermore, SOPs should be unique and therefore need to be managed in a coherent way. For instance, it is recommended that you develop a centrally coordinated numbering system to allow easy tracking of different SOPs and version numbers.

Template considerations:

- Logo and/or name of the organisation (possibly in header)
- Mention " Standard Operating Procedure"
- Footer indicating the SOP reference, version reference and the page number. Pages are numbered continuously starting at 1.

Administrative elements

- Reference to overall organisation of the SOPs (optional, *e.g.* when organised in sections, chapters, etc.)
- Reference (unique code or number)
- Version number
- Status (*e.g.* draft or final)
- Title (descriptive title of the SOP)
- Author(s) Name, signature & date
- Approvals: Name signature & date (*e.g.* head of department, quality manager)
- Effective date (date from which the SOP has to be implemented)

Content

- Introduction: a concise introduction positions the relevance of the guideline
- Objective: description of what one wants to achieve with that particular guideline
- Scope: definition of the field of application of the guideline (for instance specific to certain departments or certain activities).
- Terms and definitions: provide a reference for less common terms or terms that can have different meanings
- Responsibilities and procedure: detailed description of the actors and procedures to follow.
- Appendices: specific formats, examples, drawings, schematic presentations. Appendices are numbered, starting with 1.

YOUR LOGO **STANDARD OPERATING PROCEDURES**

Section XX	Document 01	Version 00	Draft 01
INDICATIVE TITLE			
Author	Name:	Signature	
	Date:		
Approval	Name:	Signature	
	Date:		
Approval	Name:	Signature	
	Date:		
Issue date		Effective date	

1. Introduction
2. Objectives of this procedure
3. Scope
4. Terms and definitions
5. Responsibilities and procedure
6. References
7. Appendices

Appendix 1	Tables, forms etc. that are standard used
Appendix 2	