Addressing Biosafety and Regulatory Issues Throughout the Product Life Cycle of a GM Crop

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Abstract

Products of genetic engineering have been identified as a special class that may potentially cause harm to human health and the environment. This paper presents a review of the consequences of this classification and the related regulatory requirements during the product life cycle of a genetically modified (GM) crop. The life cycle is divided into 4 stages, namely exploratory research, development, large-scale deployment and product discontinuation. For each stage, the extent to which regulatory requirements influence project decisions is reviewed, which regulatory approvals are required, which studies/activities must be foreseen, which material must be produced, and the need for specific documentation. A realistic evaluation of the required commitment to a GM crop acknowledges that any large-scale deployment does not mark the end of regulatory activities, but rather should be seen as a transition to maintenance activities and eventually product discontinuation. In addition to a longer commitment in time, several aspects are identified that require necessary financial support until discontinuation. Finally it is demonstrated that each product life cycle stage requires tight planning and coordination. Starting with the design of the construct for transformation leading to transgenic events targeted for large-scale deployment, activities must be rigorously planned for the timely collection of information and in a format acceptable to authorities. For projects involving many parties, planning, coordination and management are even more crucial. Depending upon the type of developer (large corporations, small companies, humanitarian aid projects or academic groups) and the target market for the crop/trait combination (global markets, local relevance, niche markets), different approaches may be followed. Irrespectively, the components reported in this paper will still need to be addressed. Challenges when facing global markets should provide further impetus to streamlining of GMO regulatory frameworks and a return to the fundamental question of whether these GMO-specific requirements are justified.

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Riassunto

I prodotti di ingegneria genetica sono stati identificati come una classe speciale che potenzialmente potrebbe causare danni alla salute umana e all'ambiente. Questo articolo presenta una revisione delle conseguenze di questa classificazione e le relative richieste normative durante il ciclo di vita di una coltura geneticamente modificata (GM). Il ciclo di vita si divide in 4 fasi, vale a dire la ricerca esplorativa, lo sviluppo, la diffusione su larga scala e la sospensione del prodotto. Per ogni tappa viene rivista la misura in cui le richieste normative influenzano le scelte del progetto, quali autorizzazioni normative sono necessarie, quali studi/attività devono essere previsti, quale materiale deve essere prodotto, e la necessità di una documentazione specifica. Una valutazione realistica dell'impegno richiesto in caso di una coltura GM riconosce che qualsiasi distribuzione su larga scala non segna la fine delle attività di regolamentazione, piuttosto una transizione verso attività di tutela fino, eventualmente, alla sospensione del prodotto. In aggiunta ad un impegno più lungo nel tempo, vengono qui presi in considerazione anche gli aspetti che richiedono necessariamente un sostegno finanziario. Infine, è stato dimostrato che ogni fase del ciclo di vita del prodotto richiede pianificazione e coordinamento limitati. A partire dalla progettazione del costrutto per la trasformazione che porta ad eventi transgenici destinati alla distribuzione su larga scala, le attività devono essere rigorosamente previste al fine di una raccolta tempestiva delle informazioni e in un formato accettabile per le autorità. Per i progetti che coinvolgono più Parti, la pianificazione, il coordinamento e la gestione sono cruciali. Possono essere seguiti diversi approcci a seconda di chi sviluppa il progetto (grandi aziende, piccole imprese, progetti di aiuto umanitario o gruppi accademici) e del mercato di riferimento per quanto riguarda la combinazione coltura/caratteristica (mercati globali, di rilevanza locale, mercati di nicchia). Ad ogni modo, ciascun componente riportato in questo articolo dovrà essere ulteriormente approfondito. Inoltre, le sfide su cui si confrontano i mercati globali dovrebbero fornire ulteriore impulso alla razionalizzazione dei quadri normativi sugli OGM, e un ritorno alla questione fondamentale se i requisiti OGM-specifici trovano oppure no una loro giustificazione.

1. INTRODUCTION

Traditional breeding, based on arbitrary intra-specific crosses, will be insufficient to respond to the rapidly increasing global need for more high quality food and alternative uses for crops that must be produced with limited expansion of cultivated land, impact on the environment and use of natural resources. In a recent joint publication, the OECD and the Food and Agriculture Organization of the United Nations (2013) indicated that global agricultural production is expected to grow at an average of 1.5 % annually during the period 2013-2022, compared to 2.1 % in the previous decade. The slower growth will be exhibited by all crop sectors and livestock production. In addition, the OECD has stressed that the twin policy challenge of ensuring global food security and improving environmental performance requires raising the environmental and resource productivity of agriculture, enhancing land management practices, minimising pollution discharges, curtailing damage to biodiversity, and strengthening policies that avoid the use of production and input subsidies damaging to the environment (OECD, 2013).

The performance potential of crops remains a crucial element in food security and crop production. As scientific and technological progress was made, breeding methods have been enhanced (e.g. by the use of molecular markers) and further expanded (e.g. by man-induced mutations and using rescuing techniques to allow otherwise non-viable offspring to survive). Further, using insights of the molecular and biochemical basis of phenotypical traits, breeding gained predictive and analytical power. The preciseness and broad applicability of genetic engineering has complemented traditional breeding and has facilitated the introduction of previously-inaccessible desired traits. Now, nearly 3 decades after the first field trials of genetically engineered plants, the experience with large-scale deployment of biotechnology crops confirms the success of combining specific traits that can only be introduced via genetic engineering with excellent germplasm adapted to local needs and taste. Irrespective of these achievements, products of genetic engineering have been identified as a special class of products that may potentially cause harm to human health and the environment. This review will not discuss the arguments of such special classification; rather it presents a review of the consequences of this classification and the related regulatory requirements during the life cycle of a genetically modified (GM) crop, in particular in relation to the documentation of its safety and compliance with related legislation.

2. LEGAL FRAMEWORKS FOR ACTIVITIES WITH GMOS

Driven primarily by Article 8(g) of the Convention on Biological Diversity (United Nations, 1992), many governments have or are in the process of establishing regulatory frameworks for the safe handling of genetically modified organisms (GMOs). National initiatives have been boosted by international agreements (e.g. the Cartagena Protocol on Biosafety [Secretariat of the Convention on Biological Diversity, 2000]) and capacity building programs (e.g. by the United Nations Environment Programme [UNEP]-Global Environment Fund [GEF]). Depending upon the prevailing national policy, different legal approaches have been taken ranging from handling GMOs under existing legislation to setting up GMO-specific legislation. Also the scope of the legislation differs between countries covering one of more of the following aspects: working in containment (e.g. in laboratories, growth rooms and greenhouses), confined environmental release (e.g. confined field trials), unconfined or large-scale release (e.g. commercial introduction and cultivation), import, export, food and feed use. For the exact legislative scope one must refer to the original legislation, but information can also be obtained via the Biosafety Clearing House (http://bch.cbd.int), Cartagena Protocol National Focal Points and/or the competent national authorities (http://bch.cbd.int/database/compiled-national-contacts).

Irrespective of the differences, all of these regulatory frameworks aim to ensure the safe handling of GMOs. In line with the precautionary approach, these frameworks demand the carrying out of a thorough risk assessment before an activity with a GMO is conducted and implementing risk management measures when deemed necessary. Usually this process is verified during an independent review by a national competent authority and confirmed with a formal official approval. Macdonald (2011) concludes that while the implementation of regulatory programmes, legal frameworks and regulations may differ from country to country, the information that informs the risk assessments that underlie the safe deployment of GM crops share numerous common elements and thus provides extensive opportunities for regulatory streamlining and shared or harmonised approval processes. Yet, whilst awaiting further harmonisation and mechanisms of mutual recognition, activities need to be conducted in full compliance with the locally-applicable legal requirements. Reviewing approvals for commercial releases, James (2012) reports that so far a total of 2,497 regulatory approvals involving 25

GM crops and 319 transformation events have been issued by competent authorities in 59 countries, of which 1,129 are for food use (direct use or processing), 813 are for feed use (direct use or processing) and 555 are for planting or release into the environment.

3. LIFE CYCLE OF A GM PRODUCT

Although the product life cycle of a GM crop may vary depending on the species and its use, certain phases can be distinguished based on important milestones. In this review, the product life cycle is divided in 4 stages, namely exploratory research, development, large-scale deployment and product discontinuation.

Exploratory (or basic) research addresses the function of genetic sequences including the identification of coding sequences, linking them to specific functions and traits, as well as supporting elements such as promotor and regulating sequences. Exploratory research can also target transformation methodology, enabling or improving transformation of additional species and varieties. Irrespective of the purpose, exploratory research aims to investigate a certain scientific challenge and will therefore not go beyond demonstrating "proof-of-concept" (POC), a demonstration in principle, whose purpose is to verify that some concept or theory has the potential of being used. POC can be achieved in a plant model system that is easy to transform and that requires limited space and time for evaluation (e.g. a model species such as *Arabidopsis thaliana*). Nevertheless, with increased transformation efficiency, crops of commercial interest can also be directly addressed in exploratory research. In such cases, the step to a subsequent (product) development phase may seem more imminent. Yet, the transition between exploratory research and development should be carefully evaluated as this would require that the transformation events that are produced in basic research for attaining POC also fulfil all the criteria that is required for events targeted for development. As material prepared for POC is usually not destined for the full scope of product life cycle requirements and regulatory oversight, it is advisable to make this clear distinction from the beginning, and to start any subsequent product development with a fresh round of new transformations utilising optimised genetic constructs which take into account technical, regulatory and intellectual property considerations.

During exploratory research, most activities are conducted in containment (laboratory, growth room and /or glasshouse). As some traits may be impossible to test under greenhouse conditions, confined field trials may be required. As the purpose is to establish POC as fast as possible, these confined field trials will usually be limited in: number, repetitions per trial and observations made. When POC has been demonstrated for all required elements, a development project can be initiated with the goal of delivering improved material that can be deployed on a large scale. Consequently, the targeted material should demonstrate excellent crop performance, exhibit the intended traits, have an acceptable safety profile and present a freedom-to-operate status that allows the intended use. Thus, the entire development phase is designed to make and select material, to demonstrate that these criteria are fulfilled and to obtain all necessary confirmations that the material can be used. Assuming that transformation with a redesigned genetic construct will be included, this phase will involve activities in laboratories, growth rooms and glasshouses to produce a large set of transformation events. During subsequent generations involving glasshouse and field evaluations, elite transformation events will be selected based on crop-specific criteria, expression of the introduced trait(s) and absence of unacceptable side effects. As the number of selected events decreases, testing usually expands from single locations to multi-location trials to allow evaluation under diverse conditions. This process is very similar to what is known from selection procedures in plant breeding and provides a reliable indication of crop performance.

Eventually, only a limited low number of elite events are targeted to become future products. Backcrossing to other genetic backgrounds and germplasm may start in parallel with elite event selection in order to provide different varieties adapted to specific conditions. In vegetatively-propagated crops like potato and banana, this crossing is not feasible and therefore multiple transformations and elite event selection may be required to deliver the desired range of germplasm diversity. Depending upon the country and the crop, varieties may need to be registered and protected (e.g. via breeders rights). Although this is similar to other traditionally-bred varieties, special conditions may prevail if the varietal distinction is based upon a genetically engineered trait. The final step of development will also include a gradual multiplication of plant material in preparation for large-scale use and a conclusion of the regulatory procedures allowing large-scale deployment.

Large-scale deployment is marked by distribution, cultivation and use of plant material with the newly-introduced trait. During this phase, it is usual for a routine, repetitive production of material (e.g. seeds) to be undertaken so that the varieties remain on the market over the years. Also new varieties may be further developed by continued breeding and possibly by combination with other transformation events. So-called "stacked" events, resulting from the cross-breeding of independent transformation events, offer opportunities to combine traits of interest, and several products have been successfully developed for crops like maize and cotton. Large-scale deployment also marks the rapid expansion of the type of uses. Whereas during development all material is reserved for selection and testing, large-scale deployment provides access to a broad and diverse group of users including those interested in downstream uses as food, feed, fibre and other applications. The GM crop and its downstream products enter the product chain with all its ramifications, including potentially international trade. Finally, should the product prove advantageous, market penetration may increase, with additional countries authorising cultivation of the GM crop.

While large-scale deployment is the primary target of a development project, the life cycle continues to its natural conclusion by entering a formal discontinuation phase. The discontinuation phase is triggered by the proprietor's decision to stop supporting a product on the market. It can be inspired by the launch of a new improved product, requiring the redirection of supporting efforts. It should not be confused with product withdrawal, which is typically required due to a safety or a regulatory requirement and which requires more active channelling to ensure the rapid removal of product traces. Still, as a consequence of a voluntary product discontinuation decision, communication with the users and authorities as well as the active management of remaining stocks will be required.

4. BIOSAFETY AND REGULATORY ISSUES ASSOCIATED WITH GMO LIFE CYCLE STAGES

Recognising that each of the life-cycle stages described above can be further dissected, this rough division will be used to position biosafety and regulatory requirements. For each stage, how these requirements influence project decisions, which approvals are required, which studies/activities must be foreseen, what material needs to be produced, and the need for documentation will all be reviewed. For ease of presentation, reference is made to the 'developer' as the party that will need to deal with these aspects. However, this can involve several organisations and they may change over the lifecycle of a GM crop. Involving additional parties leads to more complexity and as the described tasks are expected to be performed irrespective of the project product team composition, a clear allocation of responsibilities is required.

When collecting information for this review, 3 distinct groups of products in advanced stages could be discriminated:

- Products of commodity crops (e.g. maize, soya bean, cotton, oilseed rape, sugar beet) with global markets and developed by large private companies. The approval status as well as the evaluation of the safety data package can be monitored. This review mainly focuses on information collected for this type of products.
- Products of less-traded crops developed by corporate as well as non-corporate developers (e.g. papaya, squash) for which deployment remains local and for which export may have to be restricted due to lack of authorisations in import markets. Where relevant, information was included in this review.
- Other products for which only limited information is available on the events, the developer and their deployment (e.g. some events in rice, poplar, tomato, sweet pepper). Due to the lack of easily-obtainable information, these products were excluded from this review.

4.1. Exploratory research

4.1.1. Decisions

To discern POC, developers recognise that only limited safety information is available and that additional containment measures may be required to compensate for the level of uncertainty that is inherent in an early research project. This is usually not a problem for activities in laboratories, growth rooms and glasshouses. Yet, even for limited confined field trials, some authorities require the submission of a basic safety data package. Whereas the research subject will determine the need for particular tests to demonstrate POC, local GM regulations may impact the decision of where such tests will be conducted and whether the project can support the additional costs associated with regulatory requirements.

4.1.2. Regulatory approvals

Depending upon the prevailing local regulatory framework, regulatory approvals for activities in containment and confined field trials may be required. Typically permits for containment facilities cover a range of projects with similar biosafety levels. In such cases, individual experiments may not need separate permits. Conversely, confined field trials are usually approved on a case-by-case basis. In addition, if basic research involves collaboration in geographically-distinct sites, transportation, possibly across national borders, may be required. In such cases, it will be necessary to verify if there are specific conditions for transportation, import and export of GM material. Also, the obligations of the Cartagena Protocol on Biosafety must be adhered to, even for material destined for use in containment (Article 18.2.b).

4.1.3. Studies/activities

For the limited scope of activities, there is usually no need to perform specific safety studies. With the focus on containment measures, the regulatory scrutiny centres on confirming that the stipulated safeguard measures are in place and effective. In the case of field trials, this may include verification of isolation distance with regard to related crops, removal of sexually compatible plants, monitoring for volunteer plants, etc.

4.1.4. Material

The material used should be in accordance with the approval. Research material in field trials is usually subject to a basic characterisation to verify identity and to allow further tracing.

4.1.5. Documentation

In addition to the research findings, care should be taken to document compliance with the prevailing legislation and any specific condition imposed by the authorisation. Furthermore, any observation of the new trait influences on the overall crop performance will be useful when considering subsequent development.

4.2. Development

4.2.1. Decisions

The most important decision is whether or not to engage in development. Assuming that an interest from potential users and markets has been identified, all the steps from transformation to introducing improved varieties with the new trait in the target markets need to be mapped out. In addition to all of the technical steps, development will be largely influenced by considerations based on the regulatory requirements. Starting with the design of the construct for transformation, developers will have to find a balance between technical and regulatory aspects. For example, some authorities have indicated that specific selectable marker systems should be abandoned or avoided. In Europe, for instance, the complete phasing out in GMOs of the presence of antibiotic resistance markers which may have adverse effects on human health and the environment was required by the end of 2008 (EU, 2001). While many authorities and experts (including EFSA [see EFSA, 2009]) agree that marker genes such as *nptII* and *aadA* used in the development of GM crops are unlikely to cause adverse effects on human health and the environment, countries such as Austria and Luxembourg have routinely used alleged uncertainty on the safety of these markers as an argument to object to the commercial release of GM crops in Europe (see the various EFSA GMO Panel Scientific Opinions available at www.efsa.europa.eu/en/gmo/gmoscdocs.htm). If technically feasible, a developer may decide to use a less efficient selection system in anticipation of smoother regulatory processing. Should such an option not exist, then justification of the choice of selectable marker used and documentation of its relative safety is likely to be required.

Similarly during elite event selection, additional criteria may be included that are not strictly necessary for achieving a good product, but that may facilitate obtaining regulatory approvals. For example, development projects may focus on identifying elite events with only a single copy of a simple and well-delineated insert of the sequence of interest. While such an insert is easier to handle during breeding, an additional benefit is the reduction of characterisation studies required by regulatory authorities. Nevertheless, if an optimally performing event appears to deviate from the proposed ideal profile (e.g. contains a more complex insertion pattern), it may still be selected if the developer is willing to undertake a more elaborate (and expensive) insert characterisation.

The time and cost associated with documenting safety and obtaining the required regulatory approvals are major factors in the development decision. Kalaitzandonakes et al. (2007) conducted a systematic review of dossiers submitted to regulatory agencies, and firm-level data on associated expenses. Accumulated costs were shown to be between US$ 6.2 - 15.5

million, depending on the trait/cop combination and the calculation of overhead costs. Similar figures were indicated in a COGEM report (2008). McDougall (2011) concluded that the cost of discovery, development and authorisation of a new plant biotechnology trait introduced between 2008 and 2012 was US$ 136 million, with regulatory testing and registration accounting for over 25 % of these costs (US$ 35.1 million). Additionally, it was observed that regulatory science, registration and regulatory affairs account for the longest phase in product development, estimated at 36.7 % of total time involved. While these figures differ significantly between projects, products and markets, they illustrate that the costs and timing of a development project are largely determined by tasks associated with regulatory duties. Consequently, realistic budget projections, mainly influenced by regulatory requirements, will have a major impact on milestone decisions in development.

Finally, it is possible that during development information is obtained which poses additional challenges. As safety assessment is often based on a tiered approach, findings in a lower tier may require additional studies that are more expensive and time consuming. In other cases, data may be non-conclusive and require repetition of studies or performing more elaborated studies. If at any moment a negative indication would suggest a possible risk, the likelihood of obtaining authorisation will need to be re-evaluated, possibly leading to project abandonment. In this respect, biosafety indications have an overriding importance in relation to the viability of a project.

4.2.2. Regulatory approvals

During development, activities are performed in laboratories, growth rooms, and glasshouses, but predominantly in the field. Testing and selecting of elite events in realistic agronomic conditions, performing regulatory studies, and production of material for subsequent analyses are essential parts of this stage. For each of these, approvals may be required depending on the local regulatory framework. As pointed out above, transportation, import and export will also need to be considered and when confined field trials are envisaged, the Advanced Informed Agreement procedure of the Cartagena Protocol may have to be observed.

In addition to complying with those approvals for development activities, developers should also begin to anticipate regulatory requirements for large-scale introduction. Again, depending on the local regulatory framework, this may relate to environmental aspects, food and/or feed use. Some authorities (e.g. Australia, EU) have determined that for products that can be used both as food and feed, no separate large-scale approval (so-called "split" approval) can be obtained for either food or feed without proper justification. Another complicating factor is the difference in the basic unit that authorities accept in submissions. In this review it is assumed that the "event" is considered the regulatory unit, as is the case in most legal frameworks. It implies that any material derived through crosses with non-regulated material will be covered by the approval as well. It is also supported by the international coding system of unique identifiers proposed by OECD (2002, revised 2006). Yet in some jurisdictions, additional approvals may be required per derived variety. For example, since 2002 the Government of India has approved for commercial cultivation six Bt cotton events and more than 1100 Bt cotton hybrids and varieties incorporating these events.

Whereas the project may define the intended markets, it should be foreseen that once utilised on large-scale, the (derived) products will enter the value chain and may be exported to other countries. CropLife International (2013) advises developers to meet, prior to large-scale introduction, applicable regulatory requirements in key countries that have been identified in a market and trade assessment; have 'functioning' regulatory systems, and; are likely to import the new biotechnology-derived plant products. They provide further encouragement to:

- Conduct a market and trade assessment to identify key import markets, including those with functioning regulatory systems, prior to the commercialisation of any new biotechnology product (crop by event) in any country of commercial launch. In that market and trade assessment, consultation at an early stage with the value chain for the specific crop is required. The product's introductions should be managed so that choice of production methods (i.e. coexistence) and markets (e.g. speciality, identity preservation, and global) for that crop are available and preserved.
- Meet applicable regulatory requirements in key markets prior to commercialisation of a new GM product intended for international commodity trade unless determined otherwise in the consultation with the value chain for the crop.
- Follow generally accepted best seed quality practices designed to

prevent adventitious presence of unauthorised products and minimise unintended incidental presence of products authorised in the country of production.
- Prior to commercialisation, make available a reliable detection method or test for use by growers, processors and buyers that enables crop identity verification for the intended use.
- Promptly communicate broadly and in a transparent manner with stakeholders as to its company-specific product launch stewardship policies and their implementation.

While it is in the interest of the developer that trade can continue without being hindered by the large-scale deployment, the complexity of booming regulatory requirements poses important challenges. Focussing on experience in East African countries, Komen & Wafula (2013) conclude that the degree of trade risks associated with the commercial adoption of GM crops is first and foremost an intra-regional issue. Because the majority of agricultural export trade is with other countries in the region, the authors urge for a common approach and harmonised policies toward imports and exports of GM commodities. Yet, until such harmonisation is in place, developers will need to plan for obtaining the required approvals, even in derived markets. An additional effort will be required to segregate the products, e.g. for domestic use only, so that that they will not be exported to markets where the necessary approvals have not yet been obtained.

4.2.3. Studies/activities

As for basic research, a specific effort will need to be planned to assure full compliance with regulatory conditions associated with the development stage. Yet the majority of the effort will be taken up by regulatory science and performing studies that are targeted to provide data on biosafety of the developed events. The safety data package covers both the characterisation of the GMO in comparison with controls (e.g. molecular and biochemical characterisation, agronomic performance, compositional analysis) and studies on potential impacts (human and animal health, agronomy and the environment). Some data requirements may be directly imposed through legislation and guidance documents (see Macdonald, 2012), whereas others may be identified based on problem formulation (see Gray, 2012) or other approaches for safety assessment (see Kok et al., 2010). While some data may be generally applicable for a crop (e.g. a crop biology description) or a trait (e.g. documentation of the mode of action of an insecticidal protein), part of the data package will be specific for each event. The safety data package will be composed of different sources of information including scientific literature and independent reports, yet the major part will likely be based on studies commissioned by the developer. Drawing up the development plan, different aspects will determine the timing for conducting each study:

- *Links with development activities – certain activities* can only be conducted at specific steps in the development project. For example, a genetic stability study may span several consecutive generations, so material must be collected at the exact moment in order not to miss the unique time-window.
- *Timely availability of sufficient quantities of material* – During development, increasing quantities of material are produced for a decreasing number of transformation events. Some studies (e.g. feeding studies) require a considerable amount of material. In order to guarantee purity, this may need to be produced separately from other studies. Careful planning of production and extended studies is required in order to avoid technical delays. This is definitely the case for any project step that requires field trials, as a small delay in providing planting material can lead to missing an entire growing season.
- *Acceptability of unexploited studies* – Most of the transformation events are eliminated during development for various reasons. Consequently, any study that is performed using such events will remain unexploited unless it can be used to demonstrate a more general safety feature of the trait or crop. Another exception may be studies that serve both a selection and a regulatory purpose. For example, the determination of the absence of vector backbone sequences will be part of the regulatory data package, yet usually serves also as a selection criterion. Nevertheless, expensive and time-consuming studies will only be performed on the elite event(s) that have passed the selection procedure and consequently can only be planned towards the end of the development phase.
- *Need for regular updating* – For some information (e.g. bioinformatic searches to determine the extent of insert sequence homology [if any] to sequences known to be associated with toxins and allergens), the data package should be up-to-date. Consequently, the data can only be generated shortly before submission of the data package to the authorities. However, discovering an unexpected finding of

homology with a toxin or allergen at the last moment would require further investigation and would jeopardise submission. Many developers will therefore already undertake initial bioinformatic searches when designing the construct for transformation. Should homology with unwanted sequences be identified at this stage, either the construct can immediately be redesigned to avoid any potential regulatory issue or additional studies can be scheduled to position the findings within a scientific/regulatory context. During development the bioinformatics search can be further refined and updated.

- *Need for local studies* - In spite of a data package being compiled according to internationally-accepted standards, some authorities require that certain studies are performed at the local level, and possibly by specialised national institutes. This may be due to: local environmental conditions differing from the region where the original data were generated; a divergent use of the experimental material; an interest to utilise local capacity, or; by concerns of local public acceptance.

In addition, study designs should be carefully planned. While most authorities require similar data types, the acceptable study design may differ considerably. Differences centre primarily upon the type and number of experimental entries, including the choice and number of controls; type and number of treatments; number of tested individuals; number of repetitions in trials, and number of repetitions of an experiment in different geographic zones; length of the study, and; parameters tested. As developers usually wish to avoid duplication of studies, it is important to be aware of the different regulatory data requirements in the various targeted markets, and to commission studies that integrate these differences as best as possible. Furthermore some toxicological and eco-toxicological tests may have to be conducted according to ISO or GLP standards. Regardless, studies intended for regulatory submission should be subject to appropriate quality assurance.

The data package should provide scientific information sufficient for performing the risk assessment. Legal frameworks may dictate details on how to perform and present the risk assessment, e.g. Annex III of the Cartagena Protocol provides an outline of risk assessment methodology. Should the risk assessment identify any unacceptable risk(s) and/or uncertainty/ies, these

may be first addressed by requiring a specific management programme to accompany large-scale deployment. For example, resistance development in insect pest populations has been identified as a potential undesirable risk for large-scale deployment of Bt crops. Consequently, insect resistance management schemes have been developed and required by regulatory authorities. Such management schemes have been further linked to monitoring programmes to observe any resistance development. During the development stage, developers therefore need to anticipate if activities may be required to accompany large-scale introduction and should plan the necessary preparatory steps (e.g. develop a method to monitor resistance development in pest insects).

4.2.4. Material

There has been considerable debate concerning the type of material that can be used in regulatory studies. This has, in some cases, unfortunately led to the rejection of costly studies by some authorities. Clearly, material should be representative and fit for the intended purpose of the study. If data for a specific event must be obtained, then some identification must be available (e.g. a certificate of analysis for the tested batch) to confirm the identity of the material. In other cases, it may be sufficient to perform a study with an event that shows comparable expression and exposure levels. The choice of such material must be justified. The genetic background of the event may also influence the study. Sometimes transformation events are generated in a variety that is suitable for transformation, but which has limited commercial applicability. In this case, in parallel with elite event selection, a backcross programme will aim to introgress the transgenic trait into lines of commercial interest. Consequently, the intermediate genotypes arising during the backcross programme will be difficult to compare with the parental lines as they may exhibit differences in crop performance and compositional parameters. When describing the material, the developer must therefore ensure that the pedigree is recorded and must include sufficient controls. Sometimes additional material may be required to cover different treatments, e.g. when introducing a herbicide tolerance trait, some authorities require that compositional analyses include GM material grown with and without specific herbicide treatment.

As testing is based on a comparative approach, the choice of comparator(s) must be considered with respect to the crop and the requirements of the

authorities. The EFSA Panel on Genetically Modified Organisms (2011) dedicated an entire guidance document to the selection of comparators for the risk assessment of GM plants and derived food and feed, proposing the following terminology:

- *"Conventional counterpart"* - i) in the case of vegetatively-propagated crops, the conventional counterpart is the non-GM isogenic line; ii) in the case of crops that are propagated sexually, the conventional counterpart is a non-GM genotype with a genetic background as close as possible to the GM plant.
- *"Comparator"* - this term should be used in all other cases, i.e. cases in which the comparative assessment includes genotypes which do not fit with the definition of conventional counterpart as provided above.
- *"Isogenic and near-isogenic lines"* - in the case of a GM plant, its isogenic line is the non-GM line from which the GM plant is derived. Thus, the only difference between the isogenic line and the derived GM plant is the presence of the recombinant DNA. Near-isogenic lines are lines genetically identical to the GM plant except for some loci.
- *"Negative segregant (null-segregant)"* - plants that are negative segregants lack the transgenic event and can be produced, for example, by self-fertilisation of hemizygous GM plants, or from crosses between hemizygous GM plants and non-GM plants.

Other commercial varieties may serve as additional comparators in studies. Also information can be put in context by using publically-available database (e.g. the ILSI Crop Composition Database [ILSI, 2010]). All materials in a study must be of comparable quality. For example, the developer may need to produce starting material for all entries in a test under the same conditions, rather than to source it from different origins and thereby risk observing differences related to the history of the material.

When the elite event has been identified, the developer needs to make sure that no traces of the other rejected events remain in the material that will be further developed. Unfortunately several examples of adventitious presence of development events (e.g. event GT200 in oilseed rape [Demeke et al., 2006], event LLRice601 in rice [USDA, 2006], Amadea type in potatoes [EFSA, 2012]) discovered in commercial batches illustrate that this is very challenging and requires strict procedures from the start of the project. Furthermore, it is essential that pure material is available should official references and control samples for event-specific detection techniques be required. In this latter regard, the European Union Reference Laboratory for GM food and feed defines the following (EURL, 2008):

- *"Control sample"* - the GMO or its genetic material (positive sample) and the parental organism or its genetic material that has been used for the purpose of the genetic modification (negative sample).
- *"Reference material"* - a material or substance one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials.

4.2.5. Documentation

Documenting compliance at every step of the development project establishes the track record for the event(s) that will eventually become a product. This track record is required when submitting a regulatory application for large-scale deployment. A priori interactions with authorities may also serve to identify points of interest to be addressed in the data package and risk assessment. Nevertheless, the major part of the documentation during the development phase will concern the safety data package, the risk assessment and the regulatory submissions. Developers must keep in mind the quality requirements for regulatory studies (see earlier comment on quality management systems for studies). This is also valid for the quality of data recording and reporting. In general, a report eligible for submission to a regulatory authority should be of "scientific publication" quality and the typical structure of title, summary, introduction, material and methods, conclusions and references provides an excellent outline for regulatory reports. Reports should include all necessary information that allows a full understanding of the conditions in which the data were obtained and analysed and allows the reader (i.e. experts and authorities) to understand how the conclusion proposed by the developer was made. Whenever possible, reference should be made to officially recognised protocols (e.g. observations made by breeders for variety registration or standard analytical methods for compositional parameters). Any analytical or specific method should be described in sufficient detail to

allow verification. If any array of approved methods is available, it may be useful to include a justification for the chosen method(s). The following list provides some of the points that EFSA includes in a "completeness check" for a field trial submitted as part of an application for a GM Food and Feed approval (EFSA, 2011):

- *Experimental design*

√ Specification of test materials included in field trials, including the GM plant, the conventional counterpart and/or other comparator(s) and non-GM reference varieties.
√ Blocking (e.g. completely randomised or randomised block experimental design).
√ Rationale underlying choice of locations (the different sites selected for the trials should be representative of the range of receiving environments where the crop will be grown).

- *Description of field trials, including information on -*

√ Geographical locations (including indication on a map).
√ Soil type.
√ Crop rotation(s)/crops grown in previous seasons in the same plots.
√ Management of the field before sowing.
√ Date of sowing.
√ Agronomic practices during cultivation including, but not limited to, herbicide use and other weed management practices, pest management practices, fertiliser regime, irrigation.
√ Climatic and other cultivation/environmental conditions during growth.
√ Time of harvest.
√ Conditions during harvest and storage of the harvested material.

While reports can include summary tables, some authorities require submission of raw data (possibly in an electronic format) allowing additional, independent analysis if required. It is important to consider the documentation requirements from the beginning as retrieving information after completion of a study may prove to be difficult, if not impossible.

Also, interactions with authorities including submissions and subsequent responses to questions are essential documents. As some products will require submissions in different countries, it requires an extra administrative effort to coordinate the responses. Developers need to make sure that authorities remain informed on issues that may be raised by other authorities so that each authority can appreciate the entire data package. Finally, the authorisations delivered by authorities are critical documents. They not only determine the scope of authorised uses, but in many cases they may also specify conditions for such use.

In general, a developer will need to make sure that information is archived. Depending upon the type of information and legal requirements, different archiving periods are proposed. For some legal requirements, data need to be kept for at least 10 years following the study. However, as 10 years may already be needed for development, and as the life span of a GM crop may cover several decades, it is suggested to keep information on the elite events at least for the entire life-cycle. While digital archives can to some extent replace physical data storage, such archives must fulfil several criteria to be acceptable, e.g. it must be possible to include raw data such as field notes, it must be impossible to change data/reports after entry in the archive, and the information must remain accessible irrespective of software evolution.

4.3. Large-scale deployment

4.3.1. Decisions

The regulatory decision on approved product use will also need to take into account local and international approvals. Depending upon the approval status, more conditions and restrictions may prevail. The party responsible for the market introduction will need to determine if these conditions can be met. For most projects, this will be a gradually-changing situation, as an increasing market share will likely make control over destination and use less probable. Consequently, controls that can be put in place in the early introduction of a product may not be possible during extended large-scale deployment.

4.3.2. Regulatory approvals

In principle, all of the necessary approvals should be obtained before the first introduction of a product. However, it is likely that approvals in some export countries will not yet be authorised at that time. Furthermore, as the list of countries establishing regulatory requirements is still increasing, additional approvals may be required and submissions may continue to be deposited during the life cycle of a product.

Some approvals are considered to be unlimited, whilst others are time-limited (e.g. for 5 or 10 years) and consequently they need to be renewed as long as the product is on the market. The latter will require a specific effort to ensure timely submissions and maintenance of the approval status.

Finally, irrespective of renewals, most regulations have a provision for reacting to new findings. As GM crops remain a research topic of broad interest, occasionally new findings and additional information linked to any requisite monitoring requirements are reported. Authorities must be informed of such findings, especially if they are likely to influence the prevailing risk assessment and management measures.

4.3.3. Studies/activities

Large-scale deployment usually marks an increase of the number of actors involved. Nevertheless, certain conditions need to be observed, and in order to guarantee optimal compliance with the obligations, these need to be communicated to, and understood by, all stakeholders in the product chain. For example, if an insect resistance management plan includes certain measures, then individual growers will need to be informed and encouraged (even contractually obliged, in some instances) to implement it. While each party will have specific obligations, an extra effort can be necessary for communication and coordination. For example, when the law requires specific labelling of GMO products, then the party that introduces the material may inform its clients on the exact requirements rather than assuming that everyone involved fully understands the legal obligations.

Another area that may need attention and an investment of effort is post-market monitoring (PMM), if and where required. During development, the developer may have already identified and established elements of a possible PMM plan. The authorities, most likely as a part of the approval conditions, will determine the exact scope. While different countries foresee PMM as a possible requirement, so far only the European Union requires (for both cultivation and import authorisations) an environmental PMM addressing general surveillance and, if required by the risk assessment, case-specific monitoring. PMM for food and feed aspects is far less common and has been linked to cases where the modification results in a significant change in composition or in the use of the product in food or feed. Of paramount importance, any required PMM must be carefully planned and should be properly resourced to meet the intended objectives.

Notwithstanding the availability of a safety data package that is sufficient for large-scale deployment and any associated PMM, new data may continue to emerge from the developer and third-party research. For example, cases have been reported where a more highly-detailed detailed molecular analysis of the inserted sequences was possible through the use of newly-developed techniques. Also, third parties report new findings that are sometimes presented as allegedly providing new perspectives on the risk assessment. The developer will need to position the information in relation to the risk assessment, and may need to adapt the risk management measures and/or to perform or corroborate the new findings with directed safety studies. Even without any new issues being raised, some studies may need to be repeated in order to keep the data package up-to-date. As techniques evolve and requirements are adapted, developers may have to redo studies; most likely the case during the preparation of an approval renewal submission. It would seem reasonable that a renewal should only cover information obtained since the previous approval. However, some authorities may use the renewal as leverage to obtain a complete and updated data package, only to confirm the previous conclusions.

Finally, a product discontinuation plan (see below) 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 a decision will be taken not to support the product any longer. It may seem paradoxically that even before the large-scale deployment is a fact, a plan is drawn up in anticipation of the end of the life cycle. Yet, such early planning is essential to capture all of the information that may be needed later, to involve other stakeholders from the beginning and to ensure that tools (e.g. to detect remaining product) are available.

4.3.4. Material

In this stage, most material is produced for the large-scale deployment. The producers need to ensure that the products conform to prevailing legal requirements and the conditions of the approval. In addition to maintaining the purity of the event, this may also include communication of the unique identifier, specific GMO labelling and users instructions.

Whenever regulatory studies are planned, the same considerations as discussed for 'development' (above) remain.

4.3.5. Documentation

All efforts to comply with legal conditions should be properly documented. Results from PMM must be collected and authorities may require regular reporting, e.g. the detailed PMM requirements established in the EU include indications on how and when reports need to be presented. Ideally, these reported results allow adjustment and eventually discontinuation of the PMM effort.

Whenever (potential) issues are identified that can have an effect on the prevailing risk assessment or management, authorities need to be informed. Such interactions should be properly documented, as they mark compliance as well as responsible management of the product. Given the public interest in GM crops, it may be preferable to keep authorities fully appraised on any new finding, even those with which no potential safety issue is associated.

Finally, the Product Discontinuation Plan and associated information should be stored for later reference.

4.4. Discontinuation

4.4.1. Decisions

The decision to initiate discontinuation is partly inspired by regulatory aspects. As pointed out above, potentially substantial costs associated with biosafety and regulatory aspects remain during large-scale deployment. The developer will monitor the balance between possible revenue/interest in the product and the investment required for marketing and maintenance of the approval status. With the introduction of newer products, this balance will evolve, eventually reaching a negative result. The product discontinuation plan identifies other stakeholders who may also influence the decision. Once decided, various actions must be taken and, depending on the crop, it may take several years before all planting material has been eliminated and traces in the product chain have been reduced to a level below a certain threshold.

4.4.2. Regulatory approvals

The product discontinuation decision should be openly communicated to value chain stakeholders and authorities. Discontinued product materials (e.g. seed, grain, and derived products) generally should be allowed to move through the usual channels for end use and consumption until the effort has resulted in a level below a predefined threshold. Throughout the product discontinuation phase, appropriate regulatory approvals should be maintained to allow continuation of the normal use. In this respect, the effort during early discontinuation will remain unchanged from maintenance during large-scale deployment.

A developer's internal product discontinuation process should be properly documented and verified in order to assist in discussions with regulatory authorities and stakeholders such that further presence in the product chain above a threshold can be determined as unlikely. At that point, there may be no further need for regulatory support of the product. In the EU, the register of GM food and feed includes 2 maize and 3 oilseed rape products for which a discontinuation decision has been taken, and a temporary tolerance was accepted by the authorities to allow further reduction of remaining adventitious or technically unavoidable traces.

Although approvals are no longer renewed, these products have once been accepted as safe for large-scale deployment and, lacking counter-indications, traces should not pose any threat. The fact that a decision is taken to discontinue is unrelated to safety and it would be illogic to revert the status of such material to the same level as unapproved or even withdrawn material.

4.4.3. Studies/activities

Given that the early steps during product discontinuation require maintenance of all approvals, it may also still be necessary to perform additional studies as for large-scale deployment (e.g. issue management, updating of data package). Nevertheless, it will be difficult to justify expensive, time-consuming studies while efforts are being directed to limit further distribution of the material. The main objective of the product discontinuation effort is to eliminate product inventories and prevent new exposure of the discontinued product through research, development, and/or commercial activities. The Excellence Through Stewardship initiative proposes the following, if applicable, to be part of this effort (ETS, 2011):

- Cessation of research and development efforts.
- Cessation of commercial seed production, distribution, and sales.
- Elimination of product inventories.
- Application of appropriate quality-management procedures designed to minimise the presence of the discontinued seed product in other seed products.

- Communication of discontinuation to key stakeholders.
- Varietal de-registration/de-listing.

In addition to these actions, developers and product chain stakeholders may monitor how the presence of the product evolves. This confirmation of the effectiveness of the discontinuation may help authorities to set realistic timeframes and thresholds.

4.4.4. Material

As inventories will be eliminated, hardly any material should remain. An exception may be a minimum quantity of reference material of high purity that is kept for later verification in case of an alleged discovery of the event.

4.4.5. Documentation

To facilitate product discontinuation, relevant documentation and records should be archived as appropriate throughout the product life cycle (e.g. molecular characterisation, product information, agreements, registrations, etc.). Once the decision is taken, documentation will cover all regulatory maintenance efforts as well as proof of the implementation and effectiveness of the discontinuation effort. The need to ensure proper archiving was already highlighted above, but as the discontinuation stage comes to an end, the questions if information should be kept and, if so, for how long, must be addressed. To date, there are only a few products that have reached this stage, and thus few precedents. There may be the need to establish an "international repository" (e.g. at the Biosafety Clearing House) where such information can remain available under certain conditions.

5. CONCLUSION

Whereas a few studies have addressed the impact of biosafety and biotechnology regulations on the duration and budget of GM crop development projects, this review presents an overview of the implications during the entire life cycle. While this summary is based on existing legislation as well as on experience with advanced products, some limitations need to be taken into account. First, the risk assessment approach is still developing and, although a case-by-case analysis remains the foundation, the escalation of data requirements continues. Similarly, in spite of calls for harmonisation and for mechanisms to reduce repetitive reviews, national regulatory frameworks are still booming and supra-national initiatives are scarce. Finally, most information on successful large-scale deployment is available for products in global commodity crops developed by large corporate organisations. As these factors change, the impact of biosafety and regulation on the life cycle of GM crops may change. While the reports on impact on development already highlighted the need for a substantial investment when preparing market introduction, this review stresses even more the importance of a realistic evaluation of the commitment to products in relation to:

- *Time* - large-scale deployment at the end of the development stage will not mark the end of the regulatory activities, but rather should be seen as a transition to the next stage. Further maintenance activities are required and these will carry on until the completion of discontinuation.
- *Resources* - depending upon the business model, it can be assumed that once the product is on the market, the return will be sufficient to cover maintenance costs as well as to allow recuperation of investment. Yet, as the total cost of the life cycle proves to be a difficult calculation, this can explain why it is mainly large commodity crops that have successfully completed these steps to date. This will be a more challenging consideration when forecasting the support required for humanitarian or academic programmes, in which improved crops will be distributed free of charge.
- *Management* - All life cycle stages require tight planning and coordination. Starting with the design of the construct for transformation, leading to events targeted for large-scale deployment, activities must be rigorously planned for the timely collection of

information in a format acceptable by authorities. Every project task should be positioned in relation to the overall objectives of large-scale deployment and product discontinuation. For projects involving many parties, planning, coordination and management are even more crucial. While it is seldom feasible (or desired) to have everything planned before the start of a development project, planning may identify those areas that will need to be addressed later and by whom. For example, the project can initially be evaluated based on an early product launch strategy, which would then need further refinement by the time an elite event has been selected.

Depending upon the type of developer (e.g. large corporations, small companies, humanitarian aid projects or academic groups) and the target market for the crop/trait combination (global markets, local relevance, niche markets), different approaches may be followed. Irrespectively, the components reported in this review will still need to be addressed.

So far only a few corporate developers have managed to establish the full life cycle for GM crops and this has been raised as a critique by opponents of the technology. Yet, if other organisations, including small companies, academia and humanitarian projects are to be encouraged to successfully move from exploratory research to product development, large-scale deployment and use to the benefit of farmers and society, then the challenges described in this review must be fully acknowledged. Efforts towards ensuring safety should question if they are truly enabling the safe utilisation of the technology or if instead they are prohibitive beyond scientific justification. The challenges when facing global markets should provide further impetus to the streamlining of GMO regulatory frameworks and returning to the fundamental question if these GMO specific requirements are justified.

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