CHAPTER

6

Regulatory Frameworks

ABSTRACT

The biosafety of GMOs is controlled by a range of interlinked policies and legal, administrative and technical instruments. This chapter describes how such regulations are drawn up and implemented and how they interact with other international agreements.

OUTLINE

I. INTRODUCTION

A. National Biosafety Frameworks (NBFs) and Constituent Elements

The smooth implementation of biotechnology regulations depends on a number of interlinked policies and legal, administrative and technical instruments that constitute what is commonly referred to as a National Biosafety Framework (NBF). Five distinct elements are an essential part of an NBF as summarized below.

1. Biosafety Policy

Biosafety policies are normally part of a broader set of policies related to biotechnology, industrial development, agriculture, trade, health and environmental protection. The fact that these broader policies have been created at different times, with different objectives in mind and are administered by different bodies, makes it imperative to establish national biosafety policies which lie at the interface of these other policies, thereby ensuring harmonization and the functionality of implementation mechanisms.

2. Legal Instruments

Acts or Decrees, and the complementary technical regulations and guidelines, provide the necessary legal base and authority to implement regulatory oversight. Such authority may be given by existing regulatory regimes or amending existing regimes, or by the promulgation of GMO-specific regulations *de novo* (Table 6.1).

In addition, regulatory systems establish the boundaries of regulatory oversight and enforcement; that is, they define the regulated article (product, process and application) and provide the background for the development of technical instruments such as guidelines for risk assessment and the issuing of permits. With regard to risk assessment, regulations define the breadth of the assessment; that is, whether the assessment is conducted on purely a scientific basis or whether it also includes risk/benefit analysis and consideration of ethical and socio-economic issues.

Last but not least, regulatory systems must be consistent with and in compliance with international agreements and norms (e.g., WTO, Cartagena Protocol, *Codex Alimentarius*, etc.) (see Section III.A).

3. Administrative System

An administrative infrastructure is necessary to support the implementation of regulatory systems which, in turn, involve the establishment of mechanisms for risk analysis, risk management, post-commercialization

TABLE 6.1 Approaches to setting up a National Biosafety Framework.

Regulatory options	Advantages	Disadvantages
Existing regulations	Potentially allows the regulatory scrutiny of products with novel traits developed through conventional technologies (see also Section I.C.1 on "product-based regulation").	The scope of existing legislation may be inadequate to deal with GM products OR Problems of coordination may arise from the involvement of two or more authorities with overlapping jurisdictions.
***De novo* system**	Streamlined specifically for GM products, thus addressing public concerns with regards to GMOs and derivative products.	Novel traits derived by means of conventional technology escape regulatory scrutiny on account of the narrow focus of regulation (see also section I.C.2) OR Products for which there is extensive familiarity are subject to disproportionate regulatory scrutiny.

monitoring and risk communication, as well as mechanisms to handle notifications or requests for authorization for activities pertaining to the development, use and commercialization of GMOs and derivative products.

The functionality of administrative systems depends on:

- The existence of guidelines that make the different components of the regulatory system operational;
- Access to up-to-date scientific information and expertise for risk assessment;
- Feedback mechanisms ensuring that the system responds to changing circumstances (e.g., scientific developments and public attitudes).

NBFs are essential in defining the administrative infrastructure entrusted with regulatory implementation. The remits and functions of committees that are established in the administrative infrastructure are reviewed in detail in Section II.B.

4. Monitoring Systems and Enforcement

Post-commercialization monitoring and general surveillance are mechanisms to deal with uncertainties regarding the long-term impacts, including benefits, arising from large-scale release of GMOs. Monitoring systems define the requirements for post-approval review and, if necessary, additional information for risk assessment and the conduits through

which monitoring results are communicated to relevant authorities, experts and the public. These subjects have been reviewed extensively in Chapter 2, and specifically for human and animal health and for environmental release assessments in Chapters 3 and 4, respectively. Enforcement mechanisms are also necessary to determine levels of inspections and audit, as well as for the implementation of measures to impose administrative, monetary or trade penalties.

5. *Public Involvement*

The need for public participation in, and for access to, information related to environmental issues is highlighted in Article 10 of the Rio Declaration on Environment and Development (http://www.unep.org/Documents.Multilingual/Default.asp?DocumentID=78&ArticleID=1163). The communication of regulatory procedures and decisions to the public contributes to increased public awareness and perception of the technology, and contributes to the transparency and legitimacy of the institutions involved. The role of public perception in shaping regulations and decisions regarding GMOs and GM products is analysed in detail in Chapter 5.

However, the practicalities of public involvement are not trivial and have a bearing on operational mechanisms and procedures. The latter have to address the following questions:

- How are public inputs solicited and how are comments and responses to comments recorded?
- How are public inputs reflected in regulatory decisions?

Several regulatory systems such as that of the USA make provisions for information access through public registers and public participation in advisory committees and contributions in the risk assessment process. In designing participatory systems, care should be exercised to have balanced representation of different stakeholder groups, for example academia, industry and non-governmental organizations.

A comprehensive guide to establishing an NBF is given in UNEP-GEF (2005).

B. Evolution of NBFs

As described in Chapter 1, section VI, the need for regulation in biotechnology arose from the realization that recombinant technologies were capable of creating organisms with novel characteristics for which there was little or no experience regarding potential impacts on human health and the environment. Extensive debate occurred as to whether the technology itself and its products warranted new regulations specific to biotechnology, resulting initially in guidelines which were later given the force of law.

There are two major factors that have led to the development of national regulatory frameworks: national factors and international agreements. Public and scientific pressure in the USA led to the National Institutes of Health (NIH) issuing Guidelines on Recombinant DNA Research on 23 June 1976, which provided for both physical and biological containment protocols. Four levels of physical containment governed rDNA (recombinant DNA) laboratory experiments, requiring protective measures ranging from gloves to extractor hoods and, at the highest containment level, isolated rooms with separate ventilation and water systems, lower barometric pressure and air-locks. They also provided for three levels of biological containment, requiring that organisms were purposely modified so that they could not survive outside the laboratory. Experiments involving DNA from highly pathogenic bacteria or genes coding for toxins were prohibited outright. The NIH guidelines became an international standard of reference for researchers in academia and industry. Because they, and their subsequent revisions, were adopted only after lengthy public hearings, the guidelines also reflected unprecedented public input into scientific matters.

To provide a legal basis for these guidelines, the US government enacted various laws between 1976 and 1979. The principles behind these recombinant DNA laws were taken up by Canada and the EU and form the basis for many other national GM regulatory frameworks. The worldwide debate on the safety of GM technology led to a seminal document "Recombinant DNA Safety Considerations" (OECD, 1986) and its follow-up "Safety Considerations for Biotechnology" (OECD, 1992). These documents have since influenced the development of national biosafety regulations *ab initio* and the evolution of existing regulations to cover biotechnology and its products.

C. The Regulatory Trigger

1. Product-Based Regulations

Typical examples of regulatory evolution to encompass the products of recombinant technologies are the regulatory systems of Canada and the USA. They reflect the OECD recommendation that there is no need for countries to develop new regulations for biotechnology as "there is no scientific basis for specific legislation to regulate the use of recombinant DNA organisms".

In Canada, product-based Acts (e.g., for food, feeds, fertilizers, pesticides) that pre-existed the advent of recombinant biotechnology were adapted to cover biotechnology applications as the latter were seen as merely different approaches to produce new lines within a given family of products. As a consequence, regulatory oversight is triggered when a biotechnology-derived product is considered to be novel (termed plants

with novel traits; PNTs) in the Canadian environment. The same applies for plants with newly introduced traits regardless of whether these have been introduced by recombinant or conventional technologies. Regulatory oversight is covered by the Novel Foods Regulation under the Canadian Foods and Drugs Act and is triggered whenever trait or product is considered to be novel in the Canadian environment (http://www.hc-sc.gc.ca/fn-an/legislation/acts-lois/fdr-rad/division-titre28-eng.php). An overview of the Novel Foods Regulation is given in Fig. 6.1.

The introduction of plants or micro-organisms with novel traits as a food source, and the importation of novel whole foods and food ingredients, require mandatory pre-market notification if they were previously not available in Canada or have been genetically modified from a pre-existing counterpart through a change that is considered to be major. It should be noted that the Canadian product-based regulation in biotechnology is more expansive than other product-based regulatory systems in that it also covers organisms that have been modified through non-recombinant technologies provided that the latter are considered to be novel traits or ingredients that constitute a major departure from the non-modified parent organisms. Here the crucial point is how "novelty" and "major change" are defined (see Box 6.1); see also Case Study 1, Appendix D.

In the USA, the NIH established an rDNA Advisory Committee (RAC) to assess the state of knowledge. On the basis of the recommendations of the RAC, a more relaxed set of research guidelines was published by NIH in 1983. These guidelines continue to be referenced by industry, federal and academic laboratories.

In 1983, the NIH approved the first environmental release of an organism developed using rDNA technology (ice-minus strain of the bacterium *Pseudomonas* to control freezing damage in strawberries). The release generated immense controversy for failing to prepare a statement or assessment of the environmental impact of NIH's regulatory decision as required under the National Environmental Policy Act (NEPA). Since then, all responsibility that NIH had for regulating environmental introductions of GMOs was relinquished despite the fact that it was unclear which federal regulatory agency or agencies would be responsible for such introductions.

In response to a need for clarification, the Office of Science and Technology Policy (OSTP) began a process culminating in 1986 in the "Coordinated Framework for Regulation in Biotechnology". According to this Framework, the products of rDNA technology should be regulated on the basis of the unique characteristics and features that they exhibit, not their method of production. The products of rDNA technology were considered to pose risks to human and environmental health similar to those posed by conventional products already regulated within the USA. The possibility to develop new guidelines, procedures and even

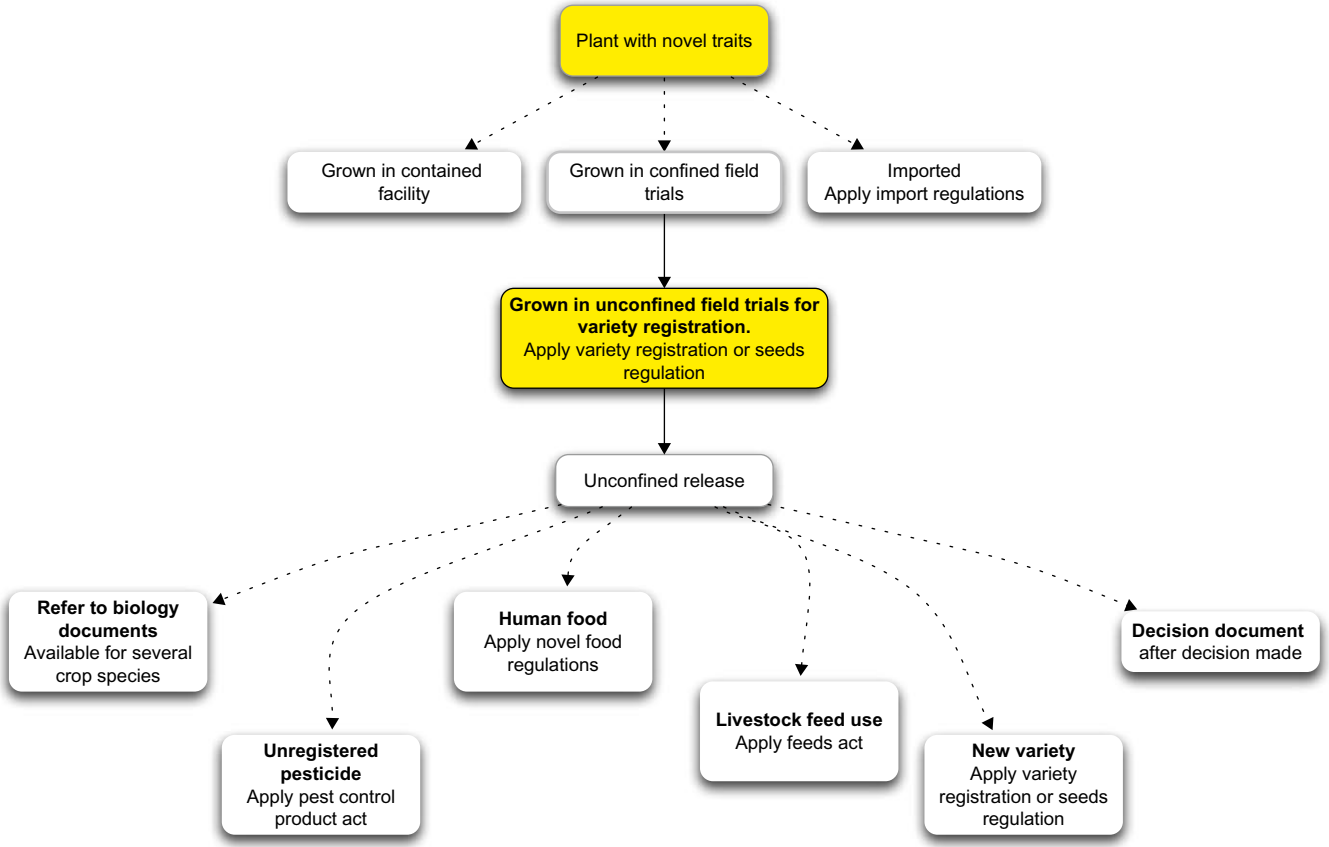

FIGURE 6.1 Diagram showing the interlinking of considerations in the Canadian Novel Foods Regulations (see colour section).

regulations to supplement or alter the scope of existing statutes was not ruled out. The Coordinated Framework identified three federal agencies as having primary responsibilities for evaluating the products of rDNA technology.

BOX 6.1

DEFINITION OF TERMS IN THE CANADIAN NOVEL FOOD REGULATIONS (HTTP://WWW.HC-SC.GC.CA/FN-AN/LEGISLATION/ACTS-LOIS/FDR-RAD/DIVISION-TITRE28-ENG.PHP)

"**genetically modify**" means to change the heritable traits of a plant, animal or microorganism by means of intentional manipulation (modifier génétiquement).

"**major change**" means, in respect of a food, a change in the food that, based on the manufacturer's experience or generally accepted nutritional or food science theory, places the modified food outside the accepted limits of natural variations for that food with regard to:

(a) The composition, structure or nutritional quality of the food or its generally recognized physiological effects;
(b) The manner in which the food is metabolized in the body; or
(c) The microbiological safety, the chemical safety or the safe use of the food (changement majeur).

"**novel food**" means:

(a) A substance, including a microorganism, that does not have a history of safe use as a food;
(b) A food that has been manufactured, prepared, preserved or packaged by a process that:
    (i) Has not been previously applied to that food, and
    (ii) Causes the food to undergo a major change; and
(c) A food that is derived from a plant, animal or microorganism that has been genetically modified such that:
    (i) The plant, animal or microorganism exhibits characteristics that were not previously observed in that plant, animal or microorganism,
    (ii) The plant, animal or microorganism no longer exhibits characteristics that were previously observed in that plant, animal or microorganism, or
    (iii) One or more characteristics of the plant, animal or microorganism no longer fall within the anticipated range for that plant, animal or microorganism (aliment nouveau).

In 1992, OSTP released another document entitled "Exercise of Federal Oversight within the Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment", outlining the proper basis by which federal regulatory agencies were expected to exercise their regulatory authority. According to this, if more than one federal regulatory agency has an interest in a particular product, lead agencies are identified as being responsible for coordinating activities to limit any potential duplication of effort.

The jurisdiction of the different agencies is shown in Table 6.2.

The jurisdiction of the regulatory agencies is determined by the regulatory mandate of the respective agencies, as well as the intended use of the GMO. Consequently, the safety review process may or may not

TABLE 6.2 Overview of responsible agencies under the coordinated framework.

Responsible agency	Jurisdiction	Regulatory trigger
Food and Drug Administration (FDA)	Food and food additives; feed and veterinary drugs	• Intentional and unintentional adulteration of food and food components with substances considered poisonous or hazardous to human health. A food or food component is considered adulterated if reasonable certainty exists that its consumption may have deleterious effects on human health. • Substances intentionally added to foods that are not generally recognized as safe (GRAS) based on prior scientific testing or historical use, or that are not otherwise exempt (e.g., pesticides, etc.). A substance may be considered as a food additive if determined to be significantly different in structure, function or amount from a substance already consumed as part of the diet or lacks a sufficient history of safe use.
US Department of Agriculture. Animal and Plant Health Inspection Agency (USDA/APHIS)	Plant pests, plants, veterinary products	• For a transgenic plant to be considered as a regulated article, any of the donor or recipient organism, vector or vector components must be in the list of plant pests or noxious weeds regulated under the Federal Noxious Weeds Act.
US Environmental Protection Agency (US EPA)	Planting and food/feed uses of pesticidal plants; new uses of existing pesticides, novel micro-organisms	• Pesticidal substances intended to be produced and used in living plants, or in plant-derived products, and the genetic material necessary for the production of such a pesticidal substance. • Genetically modified microbial pesticides, i.e. bacteria, fungi, viruses, protozoa, or algae, whose DNA has been modified to express pesticidal properties. The modified micro-organism generally performs as a pesticide's active ingredient.

involve all three agencies. Finally, it should be noted that the distinction between product- and process-based regulation is blurred in the case of transgenic plants developed through transformation technologies using *Agrobacterium* as the transformation vector. The latter is included in the list of plant pests and, therefore, any such product is regulated by USDA/APHIS.

2. *Process-Based Regulations*

In contrast to product-based regulations, process-based ones adopt a philosophy that existing legislation is not sufficient to cover products and applications arising from the use of rDNA technologies. An example of process-based regulations is that of the European Union, the operational framework of which is principally defined by Directive 2001/18/EC and a number of specific regulations. In addition, the ratification of the Cartagena Protocol effectively means the adoption of process-based regulations by over 150 countries (see below). The Protocol deals with the transboundary movement of living modified organisms (LMOs) which are defined as "any living organism that possesses a novel combination of genetic material, obtained through the use of modern biotechnology". It defines "modern biotechnology" as the "**a**. *in vitro* nucleic acid techniques, including recombinant DNA and direct injection of nucleic acid into cells or organelles, or **b**. fusion of cells beyond the taxonomic family…".

A number of process-based systems adopt the Precautionary Principle (see Box 2.3) as a guide. For example, the EU Directive 2001/18/EC explicitly adopts the Precautionary Principle and requires the evaluation of long-term and indirect effects, as well as impacts arising from changes in agricultural practice. Implicitly, however, it recognizes that the Precautionary Principle may be difficult to apply and, counterbalancing this, evokes the general principles of risk management such as proportionality, non-discrimination, consistency, and costs and benefits arising from actions or inactions. In addition, some countries (e.g., Norway, New Zealand and the EU (Commission of the European Communities, 2000)) contain options or requirements for balancing or mitigating risks associated with GM crops with potential environmental benefits arising from their cultivation. For example, GM crops with pesticidal traits may be regarded as preferable to conventional pest management with the use of chemicals with respect to impacts on non-target organisms. On the other hand, changes in agricultural practice associated with the use of herbicide-tolerant GM crops may result in more efficient weed control and, potentially, reductions in biodiversity. Consequently, this type of risk–benefit analysis must be conducted on a case-by-case basis comparing GM crop use and management with conventional agricultural practices taking into account regional differences and farming systems. This type of risk–benefit

TABLE 6.3 Comparison of process-based and product-based regulations.

Regulatory trigger	Assumptions	Advantages	Disadvantages
Process based	GM technology represents new sets of risks	Single authority offers a better coordination mechanism	Conventional products that are potentially risky can escape the net of regulation; regulation lags scientific progress leading, potentially, to overregulation.
Product based	"there is no scientific basis for specific legislation to regulate the use of recombinant DNA organisms"	Focus on phenotypic characteristics	Choice of comparator difficult and as such establishing familiarity and/or substantial equivalence difficult (see Chapter 2).

analysis requires the simultaneous operation of environmental risk monitoring and risk–benefit systems.

Socio-economic risk assessment is required in some countries (e.g. Norway (Rosendal, 2008) and the Philippines (Ochave and Estacio, 2001)) but how this is to be conducted is not always clear. Furthermore, socio-economic risk assessment in the case of importation of GM commodities would contravene the provisions of the WTO Agreement on the Application of Sanitary and Phytosanitary Measures (see below).

Advantages and disadvantages can be identified in both systems (see Table 6.3). In any case, even though the underlying philosophies of product- and process-based regulations are fundamentally different, the information requirements for risk assessment are similar and may differ only in the degree of detail, particularly in the requirements for molecular characterization (see Section II.C).

Therefore, there is a growing trend of regulatory harmonization which is achieved through international agreements and negotiations (see below) and standards-setting bodies. For example, in food safety assessment, the Canadian, EU and US systems accept as their foundation principles developed by *Codex Alimentarius* such as the comparative assessment of the GMO with its best conventional counterpart that has a known history of safe use (Paoletti *et al.*, 2008).

II. IMPLEMENTATION OF NBFS

A. Implementation Overview

NBFs set out the system by which GMOs have to be approved on safety grounds and, to this end, each GMO is subjected to science-based

risk analysis. This ensures that the release and marketing of GMOs only takes place with the explicit consent of regulatory authorities.

Regardless of the regulatory trigger, risk assessment strategies are based on a common set of principles and guidelines which are described in detail in OECD (1993) and *Codex Alimentarius* (2003), and are extensively reviewed by Paoletti *et al*. (2008).

The basic guidelines are:

- Triggers are needed to start a risk assessment;
- The assessment should follow a structured and integrated approach;
- New hazards of the GMO when compared with a conventional counterpart should be identified;
- Both intended and unintended effects of the GMO when compared with a conventional counterpart should be evaluated.

Although the implementation of NBFs varies among countries, there are a number of common elements which are summarized in Fig. 6.2.

B. The role of National Biosafety Committees

Many countries have biosafety structures that incorporate control and oversight at both the local and national levels, usually comprised of local (company or institutional) biosafety committees and a National Biosafety Committee (NBC). Some countries also have regional (state or province) biosafety committees which act between the local and national committees.

The remit of the local biosafety committee is usually to advise workers in the company or institute on biosafety matters and to oversee local adherence to biosafety regulations and conditions of controlled and contained releases. Regional biosafety committees act as a link between the local and national committees and also cover regional biosafety matters.

The NBC reviews, and conducts risk assessments on, applications for GMO releases and advises the decision makers on the biosafety issues in relation to the application. The legislation setting up most NBCs usually lays out their terms of reference, the review procedure and the mode of operation.

The terms of reference of NBCs are usually defined in national legislation, regulations or guidelines, and specify:

- The nature of the NBC, that is whether it functions as subordinate to an executive body (e.g., Ministry, Agency, etc.) and has advisory functions, or is independent having executive functions;
- The areas of competence of the NBC, for example field testing, production, importation, export and commercialization of GMOs and

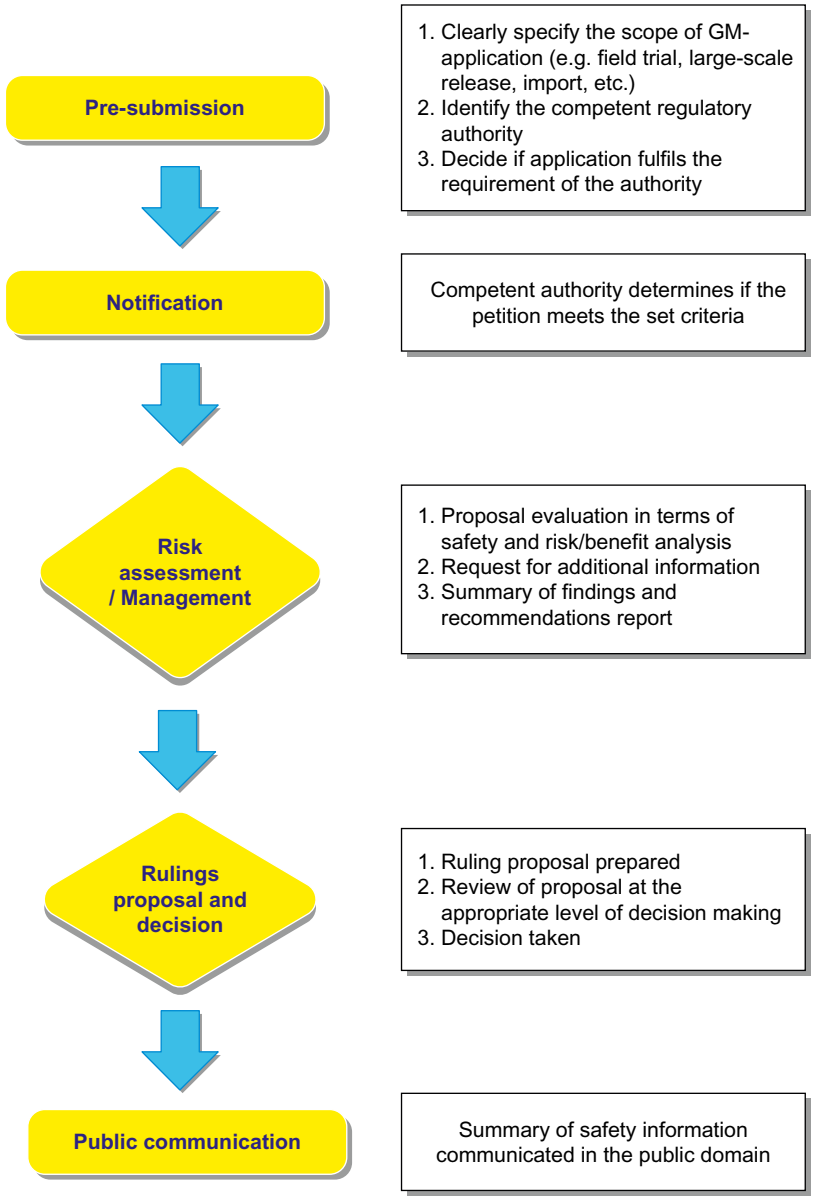

FIGURE 6.2 Common elements in NBFs assessment of applications for release of GMOs.

their derivative products. Different subcommittees may deal with each of these aspects;

- Whether reviews involve only the scientific evaluation of risks or are broader, including benefits assessment.

The review procedure usually comprises:

- Description of the context in which the review is conducted;
- Scientific evaluation of potential risks based on literature, and experimental and field trial data submitted by the applicant. Risk–benefit analyses should be subject to the terms of reference of the NBC;
- Communication of the consequences of potential risks in a decision document;
- Establishment of post-commercialization monitoring plans (if appropriate);
- Specification of the conditions under which an approval should proceed.

The mode of operation lays out:

- Rules of procedure, information management and documentation, and how conflicts of interest and confidential business information are dealt with;
- Membership of the NBC and nature of requisite expertise, for example what sort of scientific experts are needed (life and analytical sciences, ecology, agronomy), other necessary expertise (legal experts, representatives of executive bodies), and whether members of the public should be included.

C. Applying for a Release Permit

The basic regulatory framework sets out the procedures to apply for a GMO release, for the assessment of that release and for the decision making on that release.

The scope of the application will depend upon the purpose of the release. In general, for contained releases the focus will be on environmental biosafety as there will be little need for information on food and feed safety (except if there is a possibility of the GMO entering the food/feed chain). For commercial release, information will be required on both food/feed and environmental safety.

Usually, the applicant has to provide the following information on the GM product:

- Description of the recipient plant; biology of the recipient plant, uses of the recipient plant as food and/or feed, agronomy of the recipient plant;
- Description of the donor organism, for example is it a pathogen? Does it produce a toxin or allergen?
- Description of the genetic modification, including a molecular description of the construct(s), vector(s) used; gene(s), promoter(s),

terminator(s), selection marker(s), methods to determine its purity; transformation procedure;
- Description of the product, including copy number of insert, determination of site(s) of insertion; expression of RNA; expression of protein if gene inserted;
- Safety assessment of product for food and feed safety, including toxicological and allergenicity tests as described in Chapter 3; compositional analysis of key components; evaluation of metabolites; nutritional modifications; possible effects of food processing;
- Safety assessment for environmental safety as described in Chapter 4; possible gene flow to wild species in area of release, possibility of weediness, possible impact on non-target organisms;
- Description of the scope of the release; if it is a contained release, the information should include the purpose of release, site and size of release, adjacent agricultural crops, measures for containing the release (e.g., fencing, control of access), disposal of GM material, measures for cleaning up site after release finished, monitoring measures both during release and for a set period after the release, proposed actions in case of emergency. If it is a commercial release the information should include the purpose of the release, stewardship agreements between company and growers, monitoring measures.

A more detailed description of a typical guidance document for the information required to make a risk assessment is in Appendices B and C.

D. Implementation Constraints

Regulatory oversight for a single GM product lies within the area of competence of several different government authorities/agencies (e.g., Ministries of Agriculture, Environment, Health, Trade, and, on occasions, Science and Technology, etc.). More often than not, this creates problems of coordination among the different authorities, the consequences of which are delays in product approvals and escalation of regulatory costs. A recent study (Kalaitzandonakes *et al*., 2007) estimates the costs of regulatory compliance for insect-resistant corn and herbicide-tolerant corn to lie in the range of US$6–15 million, and costs related to the molecular characterization of the modified event and of stewardship plans appear to be escalating over the years. In another study (Pray *et al*., 2005), which may be more representative of the situation in developing countries with a domestic seed industry and the capacity to develop new biotechnology crops, the authors report the costs of regulatory compliance in India. The costs incurred range from US$2 to 4 million in the case of private firms and US$50 to 60 thousand in the case of government research institutions. This represents a cost reduction of almost two orders of magnitude for the public sector, which is attributable to the fact that salaries have

not been factored in and biosafety testing conducted by national institutes is done for a nominal cost. Furthermore, the years of delay to obtain release permits can be a concern. This represents a major disincentive for product development and, as such, an indirect cost of regulation. It may be one of the reasons why very few crops of direct relevance to developing world needs have been commercialized to date. Direct and indirect costs of regulation may become prohibitive and result in non-competitive market structures for biotechnology-derived products.

However, there are differences among developing countries. Broadly speaking, one can identify three tiers: those countries that have capacity to develop new technologies (see Case Study 3, Appendix D; those that have capacity to adopt technologies developed elsewhere; and those with minimal or no capacity to adopt new agricultural technologies. Inevitably, resources, infrastructure and policies differ widely among these three groups of countries, as do priorities in setting up and implementing regulations for the activities described above. Even in the more advanced developing countries, there is a lack of expertise and infrastructure to conduct science-based risk assessment. Additionally, deficits in financial resources and expertise are compounded by the lack of institutional transparency that is necessary to legitimize decisions.

E. Cooperation in GMO Regulatory Oversight Between Countries

The problem of inadequate human and financial resources to conduct science-based risk assessment could, in theory, be overcome by pooling of expertise and harmonization of risk assessment procedures at the regional and subregional level. However, in practice this has not proven possible, possibly because such an approach is seen by countries as ceding their sovereignty in taking regulatory decisions or due to differing policies regarding GMOs and/or a variety of administrative obstacles. The issue of regulatory sovereignty is debatable as obligations to international trade agreements have to be taken into account. Nevertheless, significant steps promoting international cooperation have been or are being achieved through the Advance Informed Agreement and Biosafety Clearing House Mechanisms of the Cartagena Protocol and international standards-setting bodies, such as the *Codex Alimentarius* (see Section III below).

F. Grey Areas of Regulation

Although risk assessment frameworks for GMOs are broadly similar across countries and regions, and considerable effort goes into harmonizing elements of the risk assessment where appropriate, important differences do exist among countries. Some of these differences relate back to

the distinction between regulating on the basis of process or product discussed in Section I.C, while others are more a function of the pre-existing regulatory systems that have been adapted for use with GMOs. This is not the place to describe these differences in detail but it is important to be aware that there are such grey areas of regulation.

For example, as discussed in Chapter 4, GMOs with multiple traits, known as stacked products, may be viewed in a number of ways. In particular, where multiple traits are combined through conventional breeding, regulatory systems in some countries such as Canada and the USA view the resulting product as a simple combination of the individual traits that may require little additional regulatory assessment beyond what is needed for the individual traits. The EU and some other countries regard the stacked trait combination as an entirely new product requiring a full separate assessment.

Obviously, these different approaches have significant consequences for the ability to gain regulatory approvals of stacked trait products in different countries. These sorts of differences in regulatory systems also create challenges for international initiatives aimed at harmonizing regulatory approaches.

III. BEYOND NATIONAL REGULATIONS: INTERNATIONAL INSTRUMENTS OF BIOTECHNOLOGY REGULATION

A. Multilateral Agreements

1. The Convention on Biological Diversity

The Convention on Biological Diversity (CBD) (http://www.cbd.int/convention/guide.shtml) is an international treaty, the main objectives of which are: "the conservation of biological diversity, the sustainable use of its components, and the fair and equitable sharing of the benefits from the use of genetic resources". The Convention was adopted in 1992 and has been signed and/or ratified by over 190 Parties (countries).

The Convention deals with biotechnology in two articles (Box 6.2).

The Conference of the Parties, in its 2nd meeting in Jakarta, Indonesia, in 1995, initiated negotiations to establish the protocol set out in Article 19 which resulted in the adoption of the Biosafety Protocol, also known as the Cartagena Protocol, in January 2000. Currently, there are over 150 Parties to the Protocol (see http://www.cbd.int/biosafety/signinglist.shtml).

2. The Cartagena Protocol

The Protocol focuses specifically on transboundary movements of living modified organisms (LMOs) (defined as non-processed GMOs that are viable if introduced in the environment, for example seed and

BOX 6.2

ARTICLES IN THE CONVENTION ON BIODIVERSITY RELEVANT TO BIOTECHNOLOGY

Article 8(g) contains an obligation of the Parties to "Establish or maintain means to regulate, manage or control the risks associated with the use and release of living modified organisms resulting from biotechnology which are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking also into account the risks to human health".

The first paragraph of Article 19 addresses the need for the proper handling of biotechnology and the distribution of its benefits by taking appropriate measures for "the effective participation in biotechnological research activities by those Contracting Parties, especially developing countries, which provide the genetic resources for such research, and where feasible in such Contracting Parties".

The second paragraph of Article 19 requires that the Contracting Parties "take all practicable measures to promote and advance priority access on a fair and equitable basis by Contracting Parties, especially developing countries, to the results and benefits arising from biotechnologies based upon genetic resources provided by those Contracting Parties. Such access shall be on mutually agreed terms".

The third paragraph of Article 19 requires the Parties to "consider the need for and modalities of a protocol setting out appropriate procedures, including, in particular, advance informed agreement, in the field of the safe transfer, handling and use of any living modified organism resulting from biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity".

other self-propagating material) and envisages two different procedures enabling the Parties to make risk assessment decisions. The first procedure involves an Advance Informed Agreement (AIA) applicable to LMOs that are intended to be cultivated in the country to which they are transported. The second procedure, referring to products that are intended for use as food, feed or for processing, involves the obligation to inform a central clearing house known as the Biosafety Clearing House (BCH) (Box 6.3), of any internal decision regarding marketing permits and to provide specific information, including a relevant risk assessment, to the BCH. The AIA procedure essentially requires LMOs that are transferred between two countries for the first time to obtain a "visa" before the transfer. Risk analysis

BOX 6.3

THE BIOSAFETY CLEARING HOUSE

The BCH (http://bch.cbd.int) is a mechanism set up by the Protocol to facilitate exchange of information on LMOs and to assist the Parties to better comply with their obligations under the Protocol for an Information Centre on national regulations, risk assessments and final decisions and proposes a roster of experts.

It contains a wide range of biosafety information including:

- Lists of national contacts, national laws and regulations;
- Countries' decisions on GM applications;
- Registries of LMOs (events), genes and organisms;
- Roster of experts;
- Advice on capacity building (e.g., training courses);
- A scientific bibliography database.

then may be needed in the importing country. The structure of information flow for transboundary movement of LMOs is shown in Box 6.4.

Various articles in the Protocol outline the approaches to be used by the exporting country in making the biosafety assessment and by the importing country in using that assessment (Box 6.4).

The Protocol does not prescribe any particular type of regulatory system for the exporting country. Instead, it provides countries that do not yet have domestic biosafety legislation with a legal basis to make informed decisions regarding the safety of imported LMOs and products thereof.

3. The World Trade Organization (WTO) Agreements

a. The WTO The WTO was established in 1995 as a successor organization to the General Agreements on Tariffs and Trade (GATT), primarily to administer the trade agreements associated with the latter. It provides a forum for trade negotiations and avails itself as a dispute settlement mechanism. A number of agreements administered by the WTO (Table 6.4) are relevant to the trade of GM-derived commodities and/or processed products, though none of these agreements mentions biotechnology specifically.

b. The Sanitary and Phytosanitary Measures (SPS) Agreement The most relevant Agreement is that on the Application of Sanitary and Phytosanitary Measures (SPS). This recognizes that imported and domestic

BOX 6.4

THE CARTAGENA PROTOCOL

The Protocol sets up a structure for the transference of biosafety information from a country wishing to export GMO material (LMOs) to an importing country (see Fig. 1).

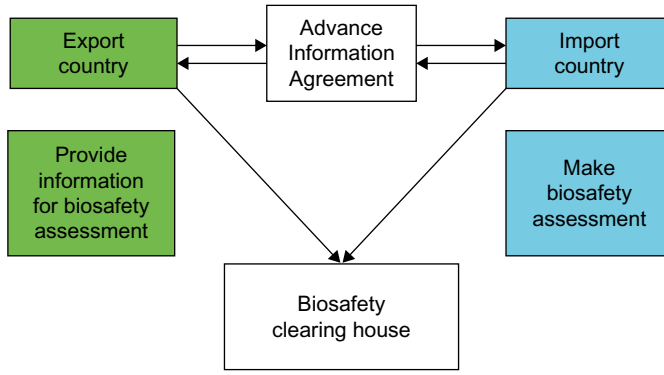

FIGURE 1 Structure for the transference of biosafety information (see colour section).

The approach that the exporting country should take to obtain the biosafety assessment information and for the importing country to assess that information is set out in various Articles in the Protocol:

Article 1 supports the Precautionary Approach (see Box 2.3) contained in Principle 15 of the Rio Declaration on Environment and Development and sets as its Objective "to contribute to ensuring an adequate level of protection in the field of the safe transfer, handling and use of living modified organisms resulting from modern biotechnology that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, and specifically focusing on transboundary movements".

Article 15 makes clear that the risk assessment procedure should be science based in stating "Risk assessments undertaken pursuant to this Protocol shall be carried out in a scientifically sound manner."

Annex III of the Protocol identifies the principles for scientific risk assessment that need to be addressed by member countries when considering LMOs that might have adverse effects on biological diversity, also taking into account the impact on human health. "Risk assessment should be carried out in a scientifically sound and transparent manner and can take into account expert advice of, and guidelines developed by, relevant

(*cont'd*)

BOX 6.4 (*cont'd*)

international organizations." It states, furthermore, that "lack of scientific knowledge or scientific consensus should not necessarily be interpreted as indicating a particular level of risk, an absence of risk, or an acceptable risk" which further enhances the Precautionary Approach.

Article 23 of the Cartagena Protocol requires public involvement in the decision-making process.

Article 26 allows for specific socio-economic issues to be taken into account in the process: "The Parties, in reaching a decision on import under this Protocol or under its domestic measures implementing the Protocol, may take into account, consistent with their international obligations, socio-economic considerations arising from the impact of living modified organisms on the conservation and sustainable use of biological diversity, especially with regard to the value of biological diversity to indigenous and local communities."

TABLE 6.4 WTO Agreements (material excerpted from a training CD-ROM on the WTO SPS Agreement prepared by the WTO Secretariat).

Agreements	Measures	Relevance to GMOs
SPS	1. Measures to protect human or animal life from additives, contaminants, toxins or disease-causing organisms in food and feed	GM crops known to pose food and feed safety risks GM crops known to contain pathogenicity elements
	2. Measures to protect animal or plant life from pests, diseases, or disease-causing organisms	GM crops known to pose risks of invasiveness
	3. Measures to protect a country from damage caused by the entry, establishment or spread of pests	Not applicable for GM crops
	4. Measures to protect human life from plant- or animal-carried diseases (zoonoses)	
TBT	Measures may be taken if proven to protect human, animal and environmental health.	Measures could be taken if a GM plant and/or products thereof are proven to be substantially non-equivalent with a non-modified counterpart.
	Measures must not be discriminatory and more trade restrictive than necessary.	Labelling of GMOs may fall under the TBT Agreement. If, however, a GM product is considered "like" a product in relation to a conventional product, then there no grounds for applying mandatory labelling.

(*Continued*)

TABLE 6.4 (*Continued*)

Agreements	Measures	Relevance to GMOs
TRIPs	Minimum level of protection for certain intellectual property (IP) rights. Inventions but not discoveries have to be patentable. Plants, animals and essential biological processes for the production of plants and animals may be excluded from patentability. IP protection is required for microorganisms, non-biological and microbiological processes.	The TRIPs Agreement may be invoked in IP protection disputes involving GM plants but not in conflicts regarding market access.
GATT	Exceptions from GATT rules can be made to protect health or the environment.	Measures could be taken if a GM crop and/or products thereof are proven to be substantially non-equivalent with a non-modified counterpart and if it can be shown that it is necessary to violate the GATT provisions in order to achieve health and environmental safety.

agricultural products need to be safe and must be devoid of risks to human, animal and plant health. For this purpose, members have the right to impose regulations protecting human and animal health (sanitary measures) and plant health (phytosanitary measures), provided that these are not applied in ways that are arbitrary and could constitute unjustifiable discrimination between countries or disguised restrictions on international trade.

Under the SPS Agreement, countries are allowed to set their own food safety and animal and plant health regulations provided that such regulations are science based and are applied only to the extent necessary for human, animal and plant health protection.

An SPS Agreement encourages Members to use international standards and guidelines. For those cases for which international standards do not exist, Members may adopt SPS measures *de novo* provided that they are scientifically justified.

The Precautionary Approach is reflected in Article 5.7 of the SPS Agreement and Members are allowed to exercise precaution provided that the measures taken are:

- Provisional (although no time limit is set);
- Adopted on the basis of "available pertinent information";
- An attempt "to obtain the additional information necessary for a more objective assessment of risk"; and
- Reviewed within a reasonable period of time.

The Agreement makes it clear that "there is a scientific justification if, on the basis of an examination and evaluation of available scientific information in conformity with the relevant provisions of this Agreement, a Member determines that the relevant international standards, guidelines or recommendations are not sufficient to achieve its appropriate level of sanitary or phytosanitary protection".

c. The Technical Barriers to Trade Agreement The WTO Agreement on Technical Barriers to Trade (TBT Agreement) also covers health protection measures, although it is different to the SPS in scope. Countries may introduce TBT measures to prevent deceptive practices and to protect human, animal, plant and environmental health. These measures concern the description of product characteristics (e.g. composition, nutritional claims, etc.) and may require product labelling and documentation related to food safety, and/or specify quality and packaging standards and regulations. They should not be more trade restrictive than necessary and should not discriminate between "like" products (i.e., imports and domestic equivalents).

d. The Role of the WTO The WTO will arbitrate on any problems arising from the trade of GM commodities between its members. Potential problems would include:

- The banning of GMOs and derivative products from importation and sales without adequate scientific justification that human and animal health are endangered;
- Applying testing and approval procedures that may be considered arbitrary and discriminatory and as such are used as unnecessary trade barriers;
- Applying labelling and identification requirements that may be considered to constitute trade barriers.

Labelling and identification requirements may become the subject of trade disputes. An increasing number of countries require or are considering the labelling of GM foods. Some other countries, most notably the USA as the largest exporter of grain and also including Canada and Argentina, require labelling for foods only if they are not substantially equivalent to their non-GM counterparts. Furthermore, at the international level, there is no common understanding as to what needs to be labelled (see Chapter 5, Section V).

Consumer demand in a number of major importing grain countries (e.g., EU, Japan) has led to "identity preservation" systems intended to completely segregate GM from non-GM foods. Such systems require traceability for the complete supply chain, from the seed and farm production stages to the delivery of the crop to the consumer ("from farm to fork"), and controls at each stage of the production and marketing

to ensure that GM and non-GM varieties are not mixed (see Chapter 5, Section V). Absolute segregation (zero tolerance) places major organizational and economic costs on grain exporters and may be considered an unjustified barrier to trade (Bullock and Desquilbet, 2002).

In the case of trade disputes involving GMOs, the interplay between the Cartagena Protocol and the relevant WTO agreements is not clear. The legal arguments are dependent on whether the GMO is introduced in the environment, used as food or feed, or derivative products are introduced into the marketplace, and on whether the disputing parties are members to the Protocol, the WTO or both. The arguments as to which agreement would play a role in dispute settlements are beyond the scope of this book and are reviewed in detail elsewhere (see Zarrilli, 2005).

B. International Standards-Setting Bodies

The role of international standards-setting bodies and international organizations acting as facilitators of regulatory harmonization in biotechnology cannot be overstated. For example, the SPS Agreement (Article 3) encourages WTO members to base their measures on international standards, guidelines and recommendations, where they exist, and recognizes three standards-setting bodies, namely the *Codex Alimentarius* Commission (http://www.codexalimentarius.net), the Commission on Phytosanitary Measures and the Office International des Epizooties. The SPS Agreement makes no legal distinction between the "standards", "guidelines" and "recommendations" of these three organizations, all of which have equal status under the SPS Agreement. The work of the *Codex Alimentarius* Commission is particularly relevant in the context of GM food safety. The *Codex* was born out of the Joint FAO/WHO Food Standards Program with the objectives of consumer protection, harmonization of food standards developed by other international bodies, and ensuring fair trade.

An *Ad Hoc* Intergovernmental Task Force on Foods Derived from Biotechnology was established under the auspices of the *Codex* in 1999. The work of the Task Force culminated in three documents: Principles for the Risk Analysis of Foods Derived from Modern Biotechnology (Principles Document), Guideline for Safety Assessment of Foods Derived from Recombinant-DNA Plants (Plant Guideline) and Guideline for Safety Assessment of Foods Derived from Recombinant-DNA Microbes (*Codex Alimentarius*, 2003).

The Principles Document is summarized by Paoletti *et al*. (2008) (Box 6.5).

Also of particular relevance is the work of the Organization of Economic Cooperation and Development (OECD). Numerous references to this have been made elsewhere in this book and the reader is referred to the website of the organization (http://www.oecd.org/department/0,3355,en_2649_34385_1_1_1_1_1,00.html).

BOX 6.5

AD HOC INTERGOVERNMENTAL TASK FORCE ON FOODS DERIVED FROM BIOTECHNOLOGY OF THE *CODEX ALIMENTARIUS* COMMISSION

Guideline Documents

This document discusses risk assessment, risk management and risk communication, and describes the safety assessment as a component of the risk assessment. The essence of the safety approach is that the new food (or component thereof) should be compared with a food already accepted as safe based on its history of safe use. The assessment should follow a structured and integrated approach. It should evaluate both intended and unintended effects, that is, intended and unintended differences from the conventional counterpart; it should identify new or altered hazards; and it should identify any changes in key nutrients that are relevant to human health. In the Guideline for the conduct of the food safety assessment of foods derived from recombinant-DNA plants the principles for risk analysis of foods derived from modern biotechnology are further detailed. For example, paragraph 4 of the Plant Guideline reiterates that rather than trying to identify every hazard associated with a particular food, a safety assessment should take a comparative approach and identify new or altered hazards relative to the conventional counterpart. Paragraph 5 of the Plant Guideline notes that if a new or altered hazard, a nutritional issue or other food safety concern is identified, one would then need to determine its relevance to human health. If all significant differences are identified and found not to pose safety concerns, then the new food can be considered to be as safe as its conventional counterpart. The framework for conducting such a safety assessment is outlined in paragraph 18 of the Plant Guideline. It states that the safety assessment of a food derived from a recombinant-DNA plant follows a stepwise process of addressing relevant factors that include:

A. Description of the recombinant-DNA plant
B. Description of the host plant and its use as food
C. Description of the donor organism(s)
D. Description of the genetic modification(s)
E. Characterization of the genetic modification(s)
F. Safety assessment:
   a. expressed substances (non-nucleic acid substances)
   b. compositional analyses of key components

(*cont'd*)

BOX 6.5 (*cont'd*)

c. evaluation of metabolites
d. food processing
e. nutritional modification
f. other considerations

References

Bullock, D.S. and Desquilbet, M. (2002). The economics of non-GMO segregation and identity preservation. *Food Policy* **27**, 81–99.

Codex Alimentarius (2003). *Codex principles and guidelines on foods derived from biotechnology*. Codex Alimentarius Commission Joint FAO/WHO Food Standards Programme, Food and Agriculture Organization, Rome.

Commission of the European Communities (2000). Communication from the Commission on the precautionary principle. Brussels, Belgium: Commission of the European Communities, 29 pp. (http://europa.eu.int/comm/dgs/health_consumer/library/pub/pub07_en.pdf)

Kalaitzandonakes, N., Alston, J.M. and Bradford, K.J. (2007). Compliance costs for regulatory approval of new biotech crops. *Nature Biotechnol.* **25**, 509–511.

Ochave, J.-M.A. and Estacio, J.-F.L. (2001). Biosafety regulation in the Philippines: salient points and pending issues. Paper delivered at the APEC-2001 Conference on Biotechnology, September 6, 2001, Bangkok, Thailand.

OECD (1986). Recombinant DNA safety considerations. http://dbtbiosafety.nic.in/guideline/OACD/Recombinant_DNA_safety_considerations.pdf

OECD (1992). *Safety Considerations for Biotechnology*. Organization for Economic Co-operation and Development, Paris, France.

OECD (1993). *Safety Evaluation of Foods Derived by Modern Biotechnology, Concepts and Principles*. Organization for Economic Co-operation and Development, Paris.

Paoletti, C., Flammb, E., Yanc, W., Meekd, S., Renckensa, S., Fellouse, M. and Kuiper, H. (2008). GMO risk assessment around the world: some examples. *Trends Food Sci. Technol.* **19**, S70–S78.

Pray, C.E., Bengali, P. and Ramaswami, B. (2005). The cost of biosafety regulation: the Indian experience. *Q. J. Internat. Agricul.* **44**, 267–289.

Rosendal, G.K. (2008). Interpreting sustainable development and societal utility in Norwegian GMO assessments. *European Environ.* **18**, 243–256.

UNEP-GEF (2005). Phase 0 toolkit module: starting the project. www.unep.org/biosafety/Documents/Toolkit_for_the_Development_Project_Starting_the_Project.pdf

Zarrilli, S. (2005). International Trade in GMOs and GM Products: National and Multilateral Legal Frameworks. Policy Issues in International Trade and Commodities. Study Series No. 29. United Nations Conference on Trade and Development.

Further Reading

Jaffe, G. (2004). Regulating transgenic crops: a comparative analysis of different regulatory processes. *Transgenic Res.* **13**, 5–19.