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Chapter 1 An Introduction to Agricultural Biotechnology Regulation in the U.S.

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Abstract The regulation of agricultural plant and microbial biotechnology products in the United States of America has a rich history that reflects the challenges the federal government has faced in the development of appropriate rules and standards needed to determine their safety to humans and the environment. Several factors – the insufficient global food supply, loss or curtailment of the use of older chemistries to control pests due to risks and environmental persistence, the rising demand for safer food commodities, and the uncertainty surrounding the sustainability of agriculture in this and other countries – have added to these challenges. The chapter introduces the U.S. Coordinated Framework for the Regulation of Biotechnology ("Framework"), and the roles of its members: the U.S. Department of Agriculture (USDA), the U.S. Food and Drug Administration (FDA), and the U.S. Environmental Protection Agency (EPA) in regulating agricultural biotechnology in accordance with U.S. federal statutes. The Framework agencies use scientific, risk-based approaches in carrying out their regulatory responsibilities for the products of biotechnology. Relying on their experiences with risk assessment and risk management policies and principles for more conventional products, the Framework agencies have adapted new risk and exposure scenarios into their evaluations to ensure the safe use of these products in agriculture.

Keywords Biotechnology • Federal Food, Drug, and Cosmetic Act (FFDCA) • Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) • Food Quality Protection Act (FQPA) • Genetically engineered crops • Plant-incorporated protectants • Plant Protection Act • Regulated articles • Regulation • Toxic Substances Control Act (TSCA) • U.S. Coordinated framework

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1.1 Background

Regulatory oversight of biotechnology has been in place in the United States (U.S.) since the 1970s, although early guidance documents did not truly have the regulatory teeth to adequately handle the oversight of all the organisms being engineered for research or commercial purposes (Pizzuli 1984). Since those early days, the regulatory system in the U.S. has developed and adapted as needed to regulate microbes, plants, fungi and animals as products of biotechnology for environmental release and commercialization. For example, genetically engineered (GE) crops have been rapidly adopted in the U.S. with about 94% of soybeans, 90% of cotton, 88 % of field corn, and 55 % of canola acreages being derived from rDNA techniques (ERS 2011; Fig. 1.1). The percent adoption of other GE crops, such as sugarbeet and alfalfa, has also increased with no evidence that this trend will not continue in the U.S. and elsewhere (ISAAA 2012). The significant adoption of GE crops reflects a functioning U.S. regulatory system.

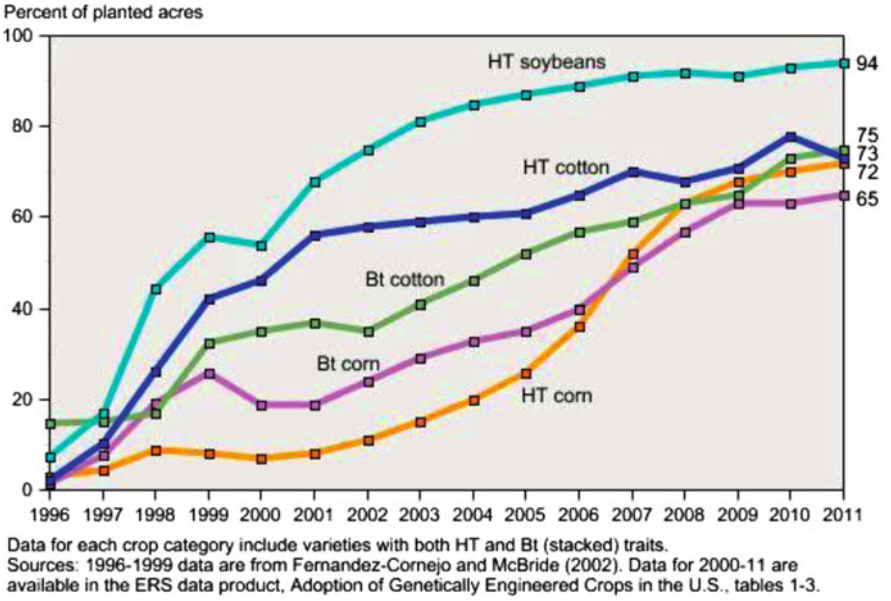

Fig. 1.1 Growth in adoption of genetically engineered crops continues in the U.S. *HT* = Herbicide tolerant, *Bt* = Expressing an insecticidal protein from *Bacillus thuringiensis*

The purpose of this chapter is to elucidate the historic guidance, regulations, and procedures that govern experimentation with genetically engineered (GE) organisms in experimental field trials and unconfined environmental release of GE organisms. The safety assessment of genetically engineered food will also be briefly discussed. All of the information for this analysis was obtained from publicly available sources provided by the respective regulatory authorities and the primary literature. The other focus of this document is the Coordinated Framework for Regulation of Biotechnology, a policy document regarding regulation of biotechnology products which was published by the Office of Science and Technology Policy (OSTP) in 1986 (OSTP 1986). The Framework involves key roles for the U.S. Environmental Protection Agency (EPA), the U.S. Department of Agriculture, Animal and Plant Health Protection Service (USDA-APHIS), and the U.S. Food and Drug Administration (FDA). This chapter restricts its focus to regulation of GE microbes and plants, while other chapters in this book examine regulation of insects and vertebrate animals.

While this book reflects the application of recombinant DNA (rDNA) to the genetic engineering of organisms, the term 'biotechnology' can be viewed more broadly to reflect the application of biology to man's needs and desires. This is especially important when making the distinction between 'genetically engineered' organisms and the more general term 'products of biotechnology' or 'genetically modified' (GM). It is worth noting that all crops plants domesticated for use by man have been modified genetically through selection and plant breeding practices. However, for the purposes of this chapter and the majority of this book, we will reserve the term as applicable to products and processes derived from the use of rDNA.

Microbial biopesticides have been regulated under FIFRA since 1948 (e.g., *Bacillus popillae*) and genetically engineered microbial pest control agents (MPCA) since the mid-1980s using the same statutory authority with regulations (40 CFR 158.2100) modified and updated over time (see Chap. 4 for more detail). It is important to note that the same regulations and data requirements were applied to both GE and non-GE MPCAs . With the advent of *in planta* expression of pesticidal substances in the late 1980s, thus creating plant-incorporated protectants (PIPs), regulations were again updated to reflect the novelty of these pesticides (EPA 1994, 2001b). Technological developments take time and regulations must remain dynamic and flexible in order to keep pace with the technology (Jepson 2003). This is certainly the case with agricultural biotechnology.

1.2 Early Regulatory Development for Biotechnology Products

For centuries, humans have improved crop plants through selective breeding and hybridization — largely through the controlled pollination of plants. Meiotic recombination following pollination that may include undesirable traits which have to be bred out of the new plant by multiple backcrosses before a hybrid can become a commercially viable new variety. In more recent times, plant breeders created new varieties using chemicals or irradiation to provide unique traits in

plants via mutagenesis. Plant transformation is a form of plant breeding with one very important difference — plant biotechnology allows for the transfer of specific genetic information from species related or unrelated to the plant with modifications to the expression pattern of these transgenes in both a temporal and spatial manner.

Traditional plant breeding involves the crossing of thousands of genes, whereas plant biotechnology allows for the transfer of only one or a few desirable genes.

Responding to the rapid increase in the production of biotechnology products, there was a realization of the need for some sort of guidance to ensure that public health and the environment are adequately protected from the potential risks of this technology. As products began moving from the laboratory toward the market, scientists and regulatory agencies realized that there should be regulatory mechanisms to ensure that these new products did not adversely affect public health or the environment (Howland 1987). To clarify regulatory jurisdiction over biotechnology products, the Reagan Administration established an interagency working group under the White House Cabinet Council on Natural Resources and the Environment (now known as the Domestic Policy Council) in 1984 and the Biotechnology Science Coordinating Committee in 1985 (Patterson and Josling 2001). The working group's principle goal was to ensure the regulatory process adequately considered health and environmental safety consequences of the products of biotechnology as they move from the laboratory to the marketplace. Safety was not their only concern; however, as the Council also emphasized the importance of not stifling innovation or enervating the competitiveness of the U.S. biotech industry. Thus, the interagency working group sought to establish a sensible framework that effectively protected human health and the environment while providing breathing room for a burgeoning industry. Scientists also wanted the freedom and flexibility to engage in research and did not want Congress to pass unduly restrictive laws (Mandel 2006).

The U.S. Federal government set forth its policy statement on the regulation of agricultural biotechnology in a document entitled the Coordinated Framework for Regulation of Biotechnology (OSTP 1986). This publication in the Federal Register established the regulatory roles for Executive Branch agencies in ensuring the safety of biotechnology research and products for human health and the environment, and in addressing a previous policy proposal promulgated in 1984 with the same title (OSTP 1984). A 2 year public comment period helped to shape this policy statement in its evolution to the final 1986 publication. The working group formed under the OSTP concluded that the existing statutes and administrative agencies would be adequate for the regulation of biotechnology as long as they were under a common framework (Stepp 1999). The Coordinated Framework for the Regulation of Biotechnology set forth policy directing the oversight of biotechnology under EPA, USDA, FDA, NIH, the National Science Foundation (NSF), and the Occupational Safety and Health Administration (OSHA) dependent on the type of genetic modification under development. The Framework also established a Biotechnology Science Coordinating Committee to ensure timely and coordinated regulatory decision making, interagency communication, discuss jurisdiction over products of biotechnology, and to keep track of the changing scene in biotechnology (Stepp 1999).

The Coordinated Framework was guided by several principles, including the concept of a case-by-case review of new products, assessing the risk associated with the product and not the process itself, and that genetically engineered organisms do not differ fundamentally from their non-GE counterparts (i.e., the same parameters of biochemistry, genetics and physiology apply to all organisms regardless of origin). It was further anticipated that the technology would evolve and regulations, as well as administrative procedures, would also need to evolve to adapt to novel products of biotechnology (OSTP 1986). It was noted early on, however, that both pesticidal and non-pesticidal microorganisms would require further regulatory refinement as compared to other organisms known at the time the Framework was released to the public.

As a result of existing statutory mandates and regulatory history, three agencies were selected to oversee the primary regulation of agricultural biotechnology: the U.S. Department of Agriculture, Animal and Plant Health Inspection Service (USDA-APHIS), the Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA). With each agency regulating products of biotechnology under separate statutory mandates, the individual product may be regulated by more than one agency (Table 1.1). It is important to remember that each agency will view the product differently based upon their statutory responsibilities. These regulatory triggers will be explained in the sections below dealing with individual agency oversight. While not discussed herein, States may also regulate these products under their laws beyond the realm of Federal mandates.

The first approved environmental release of a GE organism occurred in 1987 following the approval by the National Institutes of Health (NIH) and the U.S. Environmental Protection Agency (EPA). This first release was a field test of "ice-minus" bacteria used for preventing frost damage on strawberries (Marchant 1988). These were strains of *Pseudomonas syringae* and *Erwinia herbicola* with mutations in a gene encoding an ice-nucleation protein that is normally expressed on the bacterial cell surface, but not in "ice-minus" strains. This approval sparked a heated controversy, including several court cases, challenging the NIH decision and questioning the ability of federal agencies to address hazards to ecosystems in light of the uncertainties (Wrubel et al. 1997). Although this ice-minus phenotype is outside the normal scope of EPA oversight related to pesticides, the controversy erupting publically when the test was first proposed in 1984 and the lack of an established regulatory framework for GE organisms at that time led to EPA becoming the default agency for oversight (Bill Schneider, EPA, personal communication, 2011).

This chapter and many others in this book deal with the primary statutes which grant authority to Federal agencies for oversight of biotech products. It is at least worth mentioning that many other statutes may play a role in regulation of biotech products in specific instances at both the Federal and State levels. For example, the National Environmental Policy Act is significant in the regulatory process at USDA-APHIS and FDA (Belson 2000; Mandel 2006). The Endangered Species Act is also considered as part of the risk assessment process for USDA-APHIS, EPA and FDA when making environmental risk management decisions. Additionally, individual

Table 1.1 Oversight of genetically engineered plants and traits in the US

Trait phenotype/crop	Agency	Statutory authority[a]
Disease/insect resistance in food or feed crop	USDA-APHIS EPA/US FDA[b]	Plant Protection Act – plant pests, weeds and environmental effects FIFRA/FFDCA – PIP pesticides; environmental, food and feed safety FFDCA – food and feed safety
Herbicide tolerance in food or feed crop	USDA-APHIS[c] EPA[d] FDA	Plant Protection Act – plant pests, weeds and environmental effects FIFRA/FFDCA – herbicide use on crop; environmental effects, food and feed safety of herbicide residues FFDCA – food and animal feed safety
Herbicide tolerance in ornamental/ non-food crop	USDA-APHIS EPA	Plant Protection Act – plant pests, weeds and environmental effects FIFRA – herbicide use on crop, environmental effects
Quality enhancement traits for food or feed crop	USDA-APHIS FDA	Plant Protection Act – plant pests, weeds and environmental effects FFDCA – food and feed safety
Flower color enhancement in a non-food crop	USDA-APHIS	Plant Protection Act – plant pests, weeds and environmental effects

[a]Primary statutory authority, however, other statutes may apply under certain circumstances. It should be noted that all agencies involved are subject to the provisions of the Endangered Species Act
[b]FDA oversight may be voluntary consultation when trait is not a food additive
[c]PPA requires an assessment of the GE crop to act as a plant pest as defined in 7CFR Part 340
[d]EPA does not regulate the HT crop plant, only the use of the herbicide, and its residues on the crop and potential non-target effects from the use of herbicide in a cropping situation

states may require more restrictive regulations for biotech products as they deem fit (Beachy et al. 1996). A further discussion of these statutes influencing oversight can be found in the OSTP archived biotech case studies (OSTP 2001a).

1.3 Coordinated Federal Framework

Biotech crops undergo a food safety and environmental review process conducted by the FDA, the EPA, and the USDA-APHIS. Each agency operates under their respective laws and regulations with some statutory overlap. The three agencies routinely interact while regulating GE organisms and make an effort to keep each other apprised of regulatory findings and decisions. Additionally, the OSTP oversees the Agricultural Biotechnology Working Group (ABWG), consisting of members from the regulatory agencies as well as several other Executive branch agencies. The purpose of the ABWG meetings is to ensure coordination among the U.S.

Federal government, and to provide a forum for open and free exchange of ideas, relative to the policy, regulation and use of biotech derived products in agriculture.

Briefly, each agency's roles are as follows[1]:

- *The USDA-APHIS protects agriculture and the environment from pests, diseases, and weeds.*
- *The EPA protects human health and the environment, using the standard of no unreasonable adverse effects upon man and the environment, as it evaluates plant-incorporated protectants, microbial pesticides, and intergeneric microorganisms.*
- *The FDA protects the safety of the food and feed supply.*

1.3.1 Role of the Animal and Plant Health Inspection Service

USDA-APHIS is responsible for protecting the United States' animal and plant resources from agricultural pests and diseases. Under the authority of the Plant Protection Act (June 20, 2000), APHIS regulations (7 CFR 340) provide procedures for obtaining a permit or for submitting a notification, prior to "introducing" a regulated article in the United States. A genetically engineered organism is considered a regulated article if the donor organism, recipient organism, vector or vector agent used in engineering the organism belongs to one of the taxonomic groups listed in the regulation and is also a plant pest, or if there is a reason to believe it is a plant pest (USDA-APHIS 2001).

The act of introduction includes any movement into (import) or through (interstate) the United States, or release into the environment outside an area of physical confinement. The regulations also provide for petitions for the determination of nonregulated status. Once a determination of nonregulated status is granted, the product (and its offspring) no longer requires APHIS review for movement or release in the United States. Transgenic plants that have been genetically engineered to express insecticidal proteins are considered regulated articles by APHIS unless and until they are granted non-regulated status through the petition process.

Unlike regulatory licensing as practiced under FIFRA by EPA, once GE organisms successfully complete a deregulation process, they are no longer subject to oversight by USDA-APHIS (Mandel 2006), although they may still be regulated under FIFRA if they are PIPs. Deregulated GE plants become nonregulated and are not required to submit yearly reports on sales or distribution to USDA-APHIS as they would be required to submit to EPA if they were registered as a PIP.

APHIS regulations part 7 CFR 340.6 (c)(4) describe the types of data and information that a developer must submit in support of a petition for nonregulated status.

[1] http://www.aphis.usda.gov/publications/biotechnology/content/printable_version/BRS_CoordFrameBro.pdf

In part, these specifically include under a description of "known and potential differences from the unmodified recipient organism that would substantiate that the regulated article is unlikely to pose a greater plant pest risk than the unmodified organism from which it was derived," including effects of the regulated article on non-target organisms and indirect plant pest effects on other agricultural products and, under 7 CFR 340.6 (c) (5), data reports from field trials conducted under APHIS permit or notification that shall include "methods of observation, resulting data, and analysis regarding all deleterious effects on plants, nontarget organisms, or the environment."

Since the PPA relies on the determination of plant pest or noxious weed status as a trigger to regulation of GE organisms, and plant pests are defined rather broadly therein as essentially any organism causing harm to a plant or plant parts (Belson 2000), even the use of a plant pest (e.g., *Agrobacterium tumefaciens*) or a plant pest sequence (e.g., CaMV 35S promoter) as part of the transformation process may deem the resultant product a regulated article and under the oversight of USDA-APHIS. Interestingly, some plants engineered for herbicide tolerance while attaining the status of a noxious weed were not ultimately regulated under PPA as they were found to lack any plant pest sequences and no plant pest organism was used in their construction (USDA-APHIS 2011a, b).

1.3.2 Role of the U.S. Environmental Protection Agency

The EPA regulates pesticides under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). This Act requires that all pesticides sold or distributed in the United States must be registered with the EPA unless they are specifically exempted. The EPA also regulates the amount of pesticide residue that can be in or on the specific agricultural commodity the food or feed supply under the Federal Food, Drug, and Cosmetic Act (FFDCA). Most of this law is the purview of FDA, but the pesticidal authority to establish tolerances or exemptions from the requirement of a tolerance rests with EPA. FDA does maintain enforcement authority under FFDCA in cases where an illegal pesticide residue persists on a food or feed product.

EPA also regulates intergeneric microorganisms, under the Toxic Substances Control Act (TSCA) section 5, that are not covered by other statutes and are manufactured, imported, or processed for commercial purposes. Agricultural purposes can include biofertilizers (e.g., nitrogen fixers, mycorrhizae, phosphate solubilizers, etc.), algal biofuels, pesticidal intermediates, and perhaps, biosensors. Under the Coordinated Framework, EPA promulgated regulations for intergeneric microorganisms under TSCA which were finalized in 1997 (see Chap. 4 for greater detail).

Regulations for Biotechnology Notification prior to small scale field testing of engineered microbial pesticides were finalized in 1994 and existing regulations for PIPs were finalized in 2001. Chapter 4 in this volume contains further details on FIFRA and TSCA regulation of microbes and Chap. 10 details the regulatory requirements for PIPs under FIFRA and FFDCA.

Microbial pesticides can be naturally occurring or genetically engineered. Genetically engineered microorganisms are regulated using the same data requirements used for naturally occurring microbial pesticides (See 40 CFR part 158.740). Additional information may be required concerning the genetic engineering process used and the results from that process, however, the toxicity and pathogenicity evaluation is identical to that used to assess the non-GE counterpart MPCA. EPA requires a Biotechnology Notification be issued prior to small scale field testing of genetically engineered microorganisms at any size of environmental release to allow EPA to determine if an Experimental Use Permit is needed (See 40 CFR part 172 subpart C). When testing 10 A or more terrestrially or 1 A aquatically, EPA requires an Experimental Use Permit before field testing naturally occurring or genetically engineered microorganisms when used as microbial pest control agents (MPCA). Under FIFRA, microbial biotech products, as with all other pesticides, must be evaluated for their risks and benefits. Before any registration is granted, OPP considers such issues as potential adverse effects to non-target organisms, environmental fate of the microorganism, and the potential pathogenicity and infectivity of the microorganism to humans and other animals.

PIPs are defined as pesticidal substances "intended to be produced and used in a living plant, or in the produce thereof, and the genetic material necessary for the production of such a pesticidal substance". The PIP also includes any inert ingredient contained in the plant, or produce thereof (40 CFR 174.3). Inert ingredients may include herbicide tolerance traits and antibiotic resistance markers when they are used in the development of a PIP product. PIPs are regulated under FIFRA as pesticides and require a tolerance exemption or exemption from the requirement of a tolerance under FFDCA when the PIP is expressed within a food or feed crop (Table 1.1). The genetic material necessary for the production of such a pesticidal substance also meets the FIFRA statutory definition of a pesticide because such genetic material is introduced into the plant with the intent of ultimately producing a pesticidal effect even though the genetic material may not, itself, directly affect pests. Both the insecticidal protein and its genetic material are regulated by EPA; the plant itself is not regulated by EPA. This is a key distinction between PIP regulation by EPA and regulation of GE crops by USDA-APHIS and FDA.

EPA also issues experimental use permits (EUPs) for field trials of PIPs that are more than 10 acres cumulative area across the United States when targeting a single pest or pest complex.. These EUPs are intended to serve as a mechanism to collect field data in support of an eventual Section 3 registration. The 10 acre cutoff for regulatory oversight is based upon the concept that a small acreage results in a small overall environmental exposure and is, therefore, not likely to result in an adverse effect upon the environment. It should also be noted that in most instances, the USDA-APHIS is regulating the field trials at any size area under a permitting system. However, if the PIP could be in the food or feed supply or be fed to animals which would enter the food supply at less than 10 A area of field testing, then a tolerance or tolerance exemption must be obtained before field trials are performed regardless of whether an EUP is required or not. A company may choose to test several closely related transformation events under one EUP, but a commercial

registration would only be for a PIP resulting from a single transformation event (EPA 2011a).

PIPs are pesticides and are therefore regulated under FIFRA. Under FIFRA Section 3, EPA registers PIPs to be sold and distributed with the consequent regulations under 40 CFR. EPA evaluates each PIP application to determine whether its proposed use would cause unreasonable adverse effects on man and the environment. In order to avoid potential unreasonable adverse effects, the Agency may impose (and has imposed) conditions on registration of PIPs (e.g., conditions to slow or eliminate insect resistance; EPA 2001a). When the PIP expressing plant may enter the food or feed stream, FFDCA section 408 is also applicable to the PIP crops or human food or animal feed products derived from them.

Under FFDCA, EPA establishes tolerances, or in the case of the PIPs registered to date, tolerance exemptions, wherein no numerical maximum level or quantity of the pesticidal substance residue is denoted. Such exemptions from the requirement of a tolerance are based upon the absence of adverse toxicological outcomes during acute toxicity testing. EPA evaluates each PIP application to determine whether dietary exposure to the residue of any PIP in food or feed is safe, i.e., whether that there is a reasonable certainty of no harm resulting from aggregate exposure to the pesticide, which includes all anticipated dietary exposures and all other exposures for which there is reliable information. The tolerance exemptions issued allow PIPs to be used in foods with a reasonable certainty of no harm. Due to the ubiquitous nature of nucleic acids in food and feed, and the lack of demonstrable toxicity from their consumption, all nucleic acids as present within PIPs are exempted from the requirement of a tolerance under FFDCA.

Based on laboratory studies, field trials, and other information, EPA scientists assess a wide variety of potential effects associated with the PIP. These areas will be discussed in Chaps. 10, 11 and 12 according to scientific discipline.

EPA considers public comments for PIP regulatory actions and often holds FIFRA-proscribed Scientific Advisory Panel meetings charging outside experts to peer review EPA's risk assessments, when EPA identifies specific scientific questions or concerns that need additional consideration (EPA 2011b). All public comments are reviewed for their potential impact upon decision making (i.e., risk management) and responded to publically. Time frames and fees for EPA pesticide registration decisions vary based on the type of action. EPA uses a fee-for-service system associated with its pesticide registrations and experimental use permits under the Pesticide Registration Improvement Act (PRIA) of 2004, as amended. Under PRIA, an applicant pays a fee according to the specifics of the regulatory action sought (e.g., EUP, registration, tolerance) and receives a definitive timeline for decision making. Fees vary by action and portions of the fee may be waived depending on the affiliation of the applicant; researchers associated with a government agency will have all fees waived, those from universities or small companies may have a portion waived and those from large companies (i.e., >500 employees) will generally not receive a waiver. This fee for service approach is in contrast to FDA and USDA-APHIS who do not charge fees for reviews or consultations regarding GE microbes or plants.

1.3.3 Role of the Food and Drug Administration

The Food and Drug Administration uses the food safety and food additive authorities in the Federal Food, Drug and Cosmetic Act of 1938 (FFDCA), as amended, to regulate the safety of biotech foods. Under these laws, FDA operates a voluntary premarket notification and consultation system that provides biotech companies an opportunity to demonstrate that foods produced from their biotech crop are as safe as their traditional counterparts.

If biotech food contains a protein or other new substance that is not "generally recognized as safe" (GRAS), the food must go through a formal FDA premarket approval process in which the sponsor must prove scientifically that the new substance in the food is safe. Note that the new substance does not include pesticides, which are regulated by EPA, but rather something like a modified oil profile or a protein altered such that it is no longer an allergen.

FDA's oversight of biotech foods is managed through the Division of Biotechnology and GRAS Notice Review, Office of Food Additive Safety, in FDA's Center for Food Safety and Applied Nutrition (CFSAN), which coordinates reviews with FDA's Center for Veterinary Medicine (CVM). CFSAN regulates GE crop plants which are not PIPs and contain food additives (FDA 1997, 2005a), whereas CVM regulates GE animals containing new animal drugs (OSTP 2001b).

In 1992, the FDA issued a policy statement regarding how the agency intended to regulate human foods and animals feeds derived from new plant varieties, including varieties developed using DNA technology, which were referred to as "bioengineered foods." In general, the FDA announced that bioengineered foods would be regulated no differently than foods developed through traditional plant breeding. As a class, bioengineered foods did not require special labeling nor were they subject to premarket approval. The FDA looks to the objective characteristics of the food and its intended use, not the method by which the food was developed.

The FDA also acknowledged the food industry's long-standing practice of consulting with the FDA in the early stages of developing food through new technologies. This practice, although not required, allows the agency to identify and address issues regarding foods and food ingredients before they are marketed. The FDA expressed its expectation that such consultation would continue with regard to bioengineered foods. In 1997, the FDA issued guidance on procedures for these consultations (FDA 1997).

A company that intends to commercialize a bioengineered food meets with the FDA at an "initial consultation" to identify and discuss possible issues regarding safety, nutritional, or other regulatory issues. A "final consultation" is held once the company believes it has developed the data and information necessary to address issues or concerns raised by the FDA.

The FDA consultation process does not constitute a formal review, as would occur with a food additive for example, but rather it is a voluntary consultation. During this iterative process, the FDA Center for Food Safety and Applied Nutrition performs a comparative assessment of the composition of the GE crop and its non-GE

counterpart (FDA 1997). In instances where the proximate analysis and the examination of allergens and anti-feedants suggests that there is no significant difference between the GE and non-GE counterparts, the FDA indicates that it has no further questions regarding the use of this food or feed product in commerce, but it remains the responsibility of the manufacturer to ensure the safety of the food or feed product (Belson 2000). This finding by the FDA, while made on a voluntary basis, indicates that the GE food or feed product is 'as safe as' its non-GE counterpart. The agency does not deem a GE food or feed crop as 'safe' per se. To date, all GE food and feed products have undergone a consultation with FDA CFSAN prior to marketing even though the process is voluntary. The Flavr Savr™tomato was the first commercialized GE food crop and the only one to date to undergo formal review by FDA as a food additive, at the request or insistence of the developer Calgene (FDA 2005b). This review considered the presence of the neomycin phosphotransferase enzyme in the food product as this enzyme was used as a selectable antibiotic resistance marker in the development of the product.

1.4 Trends

The U.S. regulatory system has matured over the last 30 years by remaining adaptable and flexible as well as by being responsive to input from stakeholders. Following advances in molecular biology and rDNA techniques in the 1970s, genetic engineering of microbes, then plants, soon followed. As with most new technologies, a level of uncertainty led to apprehension among scientists and the general public once applications of biotechnology were becoming a reality (Pizzuli 1984; Griffin 1988). The Asilomar Conference in 1975 served to address some of these concerns although not all attendees were in agreement on how products of biotechnology should be regulated and by whom (Howland 1987; Marchant 1988; Barinaga 2000).

Following the establishment of the Coordinated Framework for Regulation of Biotechology in 1986, the role of the three principal regulatory agencies was somewhat clearer, however, the three agencies needed to further develop policies and practices. This was only the beginning. Guidance documents promulgated by regulatory agencies started to take shape, but these are an ongoing process to this day as they continue to respond to advances in biotechnology.

One of the authors recalls that in the late 1980s and early 1990s, even simple experiments with recombinant plasmids performed in debilitated laboratory strains of *E. coli* (e.g., K-12) triggered a laboratory inspection by both the USDA-APHIS and local university Institutional Biosafety Committee representative. Adherence to the NIG Guidelines (NIH 1976) was agreed to laboratory access limited in terms of public invitations for tours. Following applications to USDA-APHIS to receive strains of *Agrobacterium* to be used in transformation protocols, laboratory and growth room facilities were inspected and later audited to ensure all GE materials were kept confined under lock and key and uninvited personnel could not gain access to these tissue cultures bacterial stabs! Instructions were also given to placard

the doors and refrigerators with biohazard insignias. Transgenic cotton plants were not allowed in the university greenhouse, but had to be keep in a locked storage room outfitted with high intensity lamps! Early measures were rather cautious to say the least. We have come a long way since 1987.

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