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EVALUATION OF THE U.S. REGULATORY PROCESS FOR CROPS DEVELOPED THROUGH BIOTECHNOLOGY

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INTRODUCTION

Since the 1970s, researchers in universities, nongovernmental organizations, industry, and government have given a significant amount of attention to the development of new plant breeding methods based on the application of emerging techniques in molecular biology. Application of these new techniques to plant breeding has been called agricultural biotechnology, or simply "biotechnology." The term "modern biotechnology" is used specifically in reference to modern molecular breeding methods (see Glossary). Early successes in biotechnology have led to the commercial introduction of new crop varieties into which useful new traits or characteristics have been introduced. Currently, biotechnology-derived food crops approved for use in the United States include herbicide-resistant soybean, canola, corn, cotton, sugar beet, rice, and flax; insect-protected corn, cotton and potato; virus-resistant squash, potato, and papaya; and high-oleic-acid soybean (EPA 2000; EPA 2001a; FDA 2001a).

During the latter half of the 1990s, crops produced through biotechnology were adopted rapidly in the United States, with the number of acres increasing from approximately 4 million in 1996 to over 75 million in 2000 (James 2000). Farmers generally realized increased yields and/or lowered production costs. They also observed decreased use and exposure to pesticides and herbicides, reduced health risks, and diminished environmental impacts. For example, the use of *Bacillus thuringiensis* (Bt) corn, which produces its own insecticidal protein that kills European corn borers, results in increased yields and reduced reliance on chemical pesticides. Specific insecticidal proteins introduced into Bt cotton control several economically important cotton pests, resulting in significant decreases in pesticide applications in Bt cotton production. Similarly, planting herbicide-resistant soybeans or canola facilitates weed management by requiring fewer herbicide applications and promoting soil conservation through no-till weed management. The technology shows great promise, but the degree to which the technology will be sustainable, cost-effective, and beneficial

to the environment over time is dependent on variations in pest infestation levels, weather conditions, geographic regions, economic markets, and public acceptance. The feasibility of integrating biotechnology-derived crop varieties into the most economically and environmentally viable cropping systems also affects the degree to which these crops will be adopted (Carpenter and Giannessi 2001; EPA 2000; EPA 2001a).

Many scientists, government regulators, scientific societies, and science academies support the current science-based U.S. regulatory system and point to the lack of any adverse effects to either human or animal health or to the environment resulting from the use of biotechnology. They cite accumulating evidence from approximately 50 approved crops planted on more than 300 million acres worldwide. The introduction of crops produced through biotechnology has been controversial in the United States as well as in other countries (AMA 2000; APS 2001; NAS 2000). The critics of these products question the comparative food safety and environmental benefits and risks of biotechnology-derived crop varieties versus conventionally derived crop varieties. Similarly, critics and some supporters of this technology question whether new biotechnology-derived crop varieties receive sufficient regulatory review or whether they should be regulated more effectively by the U.S. government while recognizing that there are economic and social costs to regulation. The stringency and rigor of regulatory review in the United States (and other countries) should be commensurate with the established risks.

As the technology was being developed, it was generally agreed by scientists, regulators, and policymakers that plants bred with these powerful new techniques should be evaluated carefully before being put into widespread use. Therefore, under the auspices of the White House Office of Science and Technology Policy, the United States developed a *Coordinated Framework for Regulation of Biotechnology* that was published on June 26, 1986. Responsibility for implementing the *Coordinated Framework* fell to three lead agencies: the United States Department of Agriculture (USDA), the Food and Drug Administration (FDA), and the Environmental Protection Agency (EPA). The *Framework* also recognized a continuing role for the National Institutes of Health (NIH) for guidance on laboratory and greenhouse research (*Coordinated Framework* 1986).

Under the *Coordinated Framework*, all biotechnology products are subject to premarket safety assessment by at least one federal agency in accordance with existing, product-based statutes. Some crops may possess properties that make them subject to premarket safety assessment by several agencies. For example, plants remain subject to the USDA's jurisdiction, pesticidal substances in plants are regulated by the EPA, and foods and feeds are regulated by the FDA. The environmental health and safety of products are reviewed under a flexible, case-by-case approach using science-based assessment criteria intended to ensure that biotechnology products are as safe as their conventional counterparts. In the U.S. regulatory paradigm, the applicant seeking review or approval of a crop derived through modern biotechnology submits data to one or more federal regulatory agencies in support of their application or petition to proceed.

There are nine steps in the U.S. governmental safety evaluation of food and agricultural products developed using modern biotechnology. (Those steps marked with an asterisk provide an opportunity for public input.)

1. Biosafety Committee - National Institutes of Health Biosafety Guidelines*
2. USDA greenhouse standards and inspections
3. USDA field trial authorization
4. USDA authorization of transport for field trials
5. USDA determination of nonregulated status*
6. EPA experimental use permit approval*
7. EPA determination of food tolerance or tolerance exemption*
8. EPA product registration*
9. FDA review process (voluntary premarket consultation)

Biosafety committees are a requirement only for institutions that receive federal funding. Industry, however, generally complies with the NIH guidelines voluntarily but may have different standards with regard to public representation and availability of their biosafety committee meeting minutes. Biotechnology-derived crops are tested in laboratory, greenhouse, and field settings to determine the stable inheritance of the trait and that the inserted trait is expressed as intended. Then, the improved crops are evaluated to establish that they are equivalent to their conventional counterparts except for the addition of intended beneficial traits. Between 1987 and 2000, nearly 7,000 small-scale field tests were conducted under USDA regulations (ISB 2001). Following those field tests, food, feed, and environmental safety data and information on the genetic makeup of a much smaller number of plant types were submitted to the appropriate regulatory agencies for review. Before a plant product can be commercialized, the USDA must evaluate the plant product's potential impact on agriculture and the environment (Table 1). By early 2001, 49 USDA-

Table 1. Participants in the ecological safety assessment of biotechnology-derived crops

Ecological Safety Assessment of Biotechnology-Derived Crops	Participating Groups, Institutions, and Agencies
Concept review	Following NIH Biosafety Guidelines, organization proposing to develop the concept establishes a Biosafety Committee
Initial screening Early field testing Experimental use permits	USDA/APHIS EPA
Regulatory review of prescribed tests and field trial data Compositional analysis Germination/dormancy Seed bank longevity Growth and reproduction Outcrossing Assessment of fitness Field observations	USDA/APHIS
Regulatory review prescribed tests and field trial data –Plant expression studies –Specificity of expressed protein(s) –Toxicology studies Avian species—Quail Aquatic species—Catfish and daphnia (an invertebrate) Beneficial insects—Honeybee, parasitic wasp, green lacewing, ladybird beetle Soil organisms—Springtails and earthworms Mammals—Mice Environmental fate studies	EPA
Independent scientists' experiments and field trials	Land grant and other universities Private institutions Private foundations
Performance feedback –Comparisons of how biotechnology-derived crops interact with or compare to other cropping systems and the farm environment –Report observations on potential environmental impacts	Growers Agricultural extension agents Technology distributors Technology developers
Environmental stewardship	Growers Technology distributors Technology developers

approved plant products had completed the voluntary FDA premarket review process. Nineteen of these 49 biotechnology-derived plants were either insect- or virus-resistant products and also were reviewed and approved by the EPA.

Many new varieties of biotechnology-derived plants will be evaluated by U.S. regulatory agencies in the future. Some of these plants will have new agronomic and food or feed quality traits. Thousands of field tests are being conducted in the United States, and the potential exists for significant increases in the number and kind of biotechnology-derived crops available, as well as for continued expansion of planted acreage (APHIS 2001). An objective of the current paper, therefore, is to describe and evaluate the operation of the *Coordinated Framework*. This paper also poses and attempts to answer briefly the following four questions: (1) How are safety assessment and regulatory reviews conducted? (2) Can obvious strengths and weaknesses of that process be identified? (3) Can improvements be made in conduct and direction of independent research, in performance of safety assessments, in opportunities for consumer participation, or in any other aspects of the regulatory process that will both enhance the quality of the assessments and further ensure the ultimate safety of biotechnology-derived crop products? and (4) Are there improvements to the regulatory review process for biotechnology-derived plants that will enhance public confidence in the process? The requirement for brevity in this paper precludes the in-depth treatment of any specific issue. Neither is this paper intended to be a comprehensive critique of the regulatory system such as that published by the National Academy of Sciences (NAS 2000).

Premarket Environmental and Ecological Impact Safety Assessment

Existing Standards for Conventional Crops

Food derived from conventional crops generally is accepted as safe because of decades or centuries of widespread use and consumption. Similarly, experience shows that food, feed, and fiber crop varieties bred to perform in typical agricultural conditions have not invaded natural ecosystems or caused other unexpected, negative environmental impacts. Most contemporary crop varieties are the result of many years of testing for both agronomic characteristics, such as phenotypic stability, yield performance, and pest resistance, and quality characteristics, such as nutrient content, digestibility, taste, and appearance. Individual plants not meeting these criteria during the breeding and selection processes are eliminated. Historically, these well-established selection and testing procedures have provided reliable, safe crops.

Environmentally Important Criteria Evaluated for Biotechnology-Derived Crops

Crop varieties produced by biotechnology are subject to selection and testing procedures that meet and exceed those just described for conventional food, feed, and fiber crops. In fact, no premarket safety review is required for new food and fiber plant varieties produced by conventional methods. Because biotechnology-derived crops are created by adding a specific trait to existing varieties, testing and evaluation procedures focus on whether the introduced trait poses safety questions beyond those of the parental varieties and whether the new variety is materially different from or essentially the same as the parental varieties. More specifically, information about characteristics of new varieties that may have ecological effects—including growth and development characteristics, outcrossing potential and impact, toxicity to nontarget organisms, and environmental fate—is obtained and evaluated by the appropriate agency to evaluate the safety of those new varieties. The USDA Animal and Plant Health Inspection Service (APHIS) and the EPA have specific roles in evaluating this information before a variety is released. These roles are described in the following sections.

Role of the USDA/APHIS

The USDA/APHIS is responsible for assessing the environmental safety of biotechnology-derived crops under the authority of the Plant Protection Act (PPA) and the National Environmental Policy Act (NEPA). Given the authority of APHIS to regulate the movement, import, and release of plant pests or potential plant pests under the PPA, the primary focus of the APHIS review is to determine whether or not a plant produced through biotechnology has the potential to become a weed, create plant pests through outcrossing, or otherwise adversely affect natural habitats or agriculture. APHIS has guidelines covering laboratory and greenhouse research and field testing and has developed specific regulations for containment, transport, and field testing of biotechnology-derived crop varieties. The results from initial screenings in laboratory and greenhouse settings typically are included in requests to APHIS for a permit for cultivation of contained field plots. Permit requests must be submitted to APHIS at least 120 days before planting and must contain information on the introduced gene, selectable markers, safeguards to prevent dissemination or carryover of plants, and differences between the biotechnology-derived crop plant and its unmodified parent. In addition, APHIS reviews required information on the agronomic and fitness characteristics of the biotechnology-derived crop variety (Table 1).

Conditions for the conduct of field trials are tailored to the individual field test requests and are based on the relevant biological and environmental characteristics of individual crops to ensure that the regulated materials do not persist in the environment. For example, conduct of field trials for open-pollinated plants such as corn are designed differently from trials for self-pollinating plants such as soybeans. Additionally, requests for testing crops that can cross with weedy relatives, such as wild mustard species, generally result in more stringent isolation requirements than requests for testing crops with no endemic relatives, such as soybeans in North America. Once a crop is approved for testing, permit information is posted on the APHIS web site (APHIS 2001).

Permits are not required for field testing certain plants, provided that APHIS is notified in advance. To qualify for the notification process, a plant must meet six health and environmental safety requirements: (1) the plant must not be listed as either a noxious weed or a weed in the test region; (2) the introduced genetic material must be stable from generation to generation; (3) the function of introduced genetic material must be known and must not result in any plant disease; (4) the introduced genetic material must not cause the introduction of an infectious entity, must not encode substances known or likely to be toxic to nontarget organisms that feed or live on the plant species, and must not encode products intended for pharmaceutical use; (5) plant virus-derived sequences must not pose a significant risk of creation of any new plant virus; and (6) the plant must not contain genetic material from known animal or human pathogens.

The movement or release of the biotechnology-

derived plant also must meet certain performance standards including restrictions on shipping and planting; requirements for identification, containment, and a means to insure that the plants or plant parts are rendered nonviable; a prohibition on viable vector agents; and restrictions on persistence in the environment during and after field trials. In accordance with the notification process, APHIS must either acknowledge that the designated introduction activity (e.g., importation, interstate movement, or field testing) is appropriate under notification or deny permission for introduction under notification.

Once appropriate and sufficient data have been collected regarding the potential environmental impact of a biotechnology-derived plant, the developers of the plant can petition APHIS for a determination stating that a biotechnology-derived plant should no longer be regulated as a plant pest. APHIS rules contain detailed requirements for the data and information that must be included in a petition for determination of "nonregulated status." APHIS will publish a notice in the *Federal Register* and provide a 60-day public comment period for each petition that meets the eligibility criteria. To date, APHIS has approved 52 of 73 petitions submitted for nonregulated status; the remainder were withdrawn or found to be incomplete or void. (Detailed requirements for the petition can be found in 7CFR 340.6 [http://www.aphis.usda.gov/biotech/petguide.html].)

Before approving a petition for nonregulated status, APHIS must follow NEPA requirements and prepare both a publicly available environmental assessment and, if applicable, an environmental impact statement. There is a public comment period, typically 60 days, once an environmental assessment is drafted and made available to the public. Before acknowledging the appropriateness of a notification or issuing a field test permit, APHIS also must notify the state in which the release is planned.

Role of the EPA

The EPA regulates pesticides produced in biotechnology-derived plants by authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) for plant-incorporated protectants (formerly plant pesticides). An introduced protein that allows a biotechnology-derived crop to resist attack from disease or pests is classified by the EPA as a "plant-incorporated protectant" and thus is subject to the agency's regulation under FIFRA of the sale, distribution, and use of pesticides (EPA 2001b). Under FIFRA, a pesticide must not cause "unreasonable adverse effects on the environment," which by definition encompasses ecological concerns as well as human health risks. Therefore, the EPA requires detailed information on the expression, specificity, toxicology, nontarget organism, wildlife, and endangered species impacts, and environmental fate of new proteins in biotechnology-derived crops (see Table 1 in this paper and Appendix B in NAS 2000 for a detailed listing of kinds of data required). The EPA reviews this material on a case-by-case basis. A risk/benefit analysis balances potentially adverse environmental effects with proposed environmental and societal benefits, such as reducing chemical applications and ensuring an abundant, economical food supply.

There are several distinct stages in the EPA regulatory process, depending on the product involved. At each stage, the agency publishes a notice in the *Federal Register*, allowing interested parties an opportunity to submit information and express their views. According to EPA regulations, prior to initiating field trials with biotechnology-derived pesticidal crops that exceed 10 acres in size, the testing institution must apply to the EPA for an experimental use permit. These tests are conducted to generate safety information or materials for the safety assessment to be used in the approval process or to continue breeding and efficacy evaluation on a larger scale. These tests are subject to careful monitoring requirements and additional conditions, which are intended to minimize the possibility that the plants could unintentionally enter the food or feed supply or persist in the environment. In the final stage prior to full commercialization, the EPA reviews the application for the registration of the product and accepts public comments related to the plant-incorporated protectant. The EPA also may seek the counsel of external scientific experts at public meetings of its Scientific Advisory Panel or Pesticide Program Dialog Committee. Approvals for the commercial release of crops that resist insect or virus attacks are contingent on several additional requirements, such as resistance management programs. At any time during the registration process, the EPA can request additional data it deems necessary to complete the safety and risk assessment.

The federal agencies have adopted a case-by-case approach rather than a specific set of evaluations. This performance-oriented approach provides federal agencies flexibility and the authority to require extra information regarding the likelihood of ecological or human health effects associated with biologically important traits of each crop species. For example, for biotechnology-derived varieties of open-pollinating canola planted in the same region as their compatible wild relatives, more-detailed studies on the impacts of gene flow might be required than for self-pollinating soybeans in regions of North America where there are no wild relatives of soybeans.

Premarket Food and Feed Safety Assessment

Historical Perspective on the Existing Standard

The FDA is granted primary authority for the safety of the food supply by the Federal Food, Drug, and Cosmetic Act (FFDCA). Food must not be ordinarily injurious to health and must not contain any substance that may render it injurious to health. Because both "zero risk" and "absolute safety" are impossible to achieve in the food system, the legislative history of the FFDCA and, therefore, the FDA have defined the standard for food safety as a *reasonable certainty of no harm*.

With the passage of the Food Quality Protection Act in 1996, that same definition of safety applies to the EPA's review of pesticide residues in food under Section 408 of the FFDCA. Neither the law nor agency policy ever has made any distinction in the safety standard to be applied based on the source or method of production of whole foods or food ingredients. The FDA confirmed the application of that uniform standard to biotechnology-derived foods in the 1986 *Coordinated Framework*, the 1992 *Policy on Foods Derived from New Plant Varieties*, and the recently proposed mandatory premarket notification rule for bioengineered foods (*Coordinated Framework* 1986; FDA 2001b). Similarly, the EPA applies the same safety standard to pesticide residues in food, regardless of their source. Both agencies have held that it is the safety of the product, rather than the process used to produce the product, that is of greater concern (U.S. National Biotechnology 1992).

Role of the FDA and the EPA in Food Safety Assessment

The FDA and the EPA use a similar strategy for food safety evaluation. Although there are some analyses (such as composition, nutritional value, food allergy potential, or toxicity) that are performed routinely on all new products, there is no standard battery of tests specifically required for all products. Because each product is unique and poses different issues, each is evaluated on a case-by-case basis following a flow chart or "decision tree" with three key elements: (1) evaluate the safety of the source organism and genetic material used in the transformation process, (2) assess the safety of gene expression products resulting from the newly inserted genetic material, and (3) establish the safety for consumption of the whole plant or food derived from the plant.

Risks associated with DNA consumption per se are the same for DNA derived from both conventional and biotechnology-produced plants (Beever and Kemp 2000). The FDA has concluded that DNA is *generally regarded as safe* (GRAS), independent of its source, inasmuch as all DNA is composed of the same four components, which are and always have been constituents in nonprocessed or whole foods (FDA 2001b; U.S. National Biotechnology 1992). Therefore, the safety evaluation of the newly inserted DNA focuses on potential risks associated with acquisition and expression of the specific genetic information inserted into the plant if the DNA were to transfer to human, animal, or bacterial cells. The safety of DNA that encodes marker genes and its potential for transfer often is a major consideration. To date, there has been no observation in nature showing evidence for the transfer of antibiotic resistance marker genes from plants to other organisms (FAO/WHO 2001). Approval of antibiotic resistance genes has been restricted to those resistance markers for which resistance is already widespread in nature. It is recommended that the gene selected be a resistance marker to an antibiotic that is not used to a significant extent in human or veterinary medicine. It should be noted that some biotechnology-derived crops do not contain antibiotic resistance marker genes, and that new marker genes and selection strategies that reduce the need for antibiotic resistance markers are being developed (FAO/WHO 2001).

The second element of the evaluation—the safety assessment of the newly introduced trait(s) or expressed product(s)—begins with a thorough understanding of the history of safe consumption, the specificity or mode-of-action of the expressed protein, and the relatedness of the protein to other proteins that have a history of safe consumption. The protein also is evaluated for similarity to any known toxicant or allergen. Often these factors are evaluated fully before product development begins, or they are assessed very early in the development cycle. After expression levels of the gene product are evaluated, the estimated dietary intake can be calculated. Safety studies include a determination of digestibility and stability to processing. The toxicity of the newly introduced protein typically is evaluated in animal-based model systems.

Because genetic modification usually results in the introduction of new proteins into food plants, the potential allergenicity of the newly introduced proteins must be assessed. In 1996, a joint panel of experts from the International Life Science Institute and the International Food Biotechnology Council developed the first detailed scheme for assessing the potential allergenicity of biotechnology-derived crops (Metcalfe et al. 1996). In early 2001, the Food and Agriculture Organization (FAO)/World Health Organization (WHO) held an expert consultation on this issue and published a revision of the original scheme (FAO/WHO 2001). The potential

allergenicity of introduced proteins can be evaluated by focusing on these characteristics: the source of the gene; the amount of amino acid sequence similarity shared with known allergens; the expression level of the protein in the biotechnology-derived crop; the function of the novel protein; the reactivity of the protein with IgE antibodies from the serum of individuals having known allergies to the source of the transferred genetic material or similar materials (if the gene is obtained from a known allergenic source); and various physicochemical properties of the newly introduced protein, such as heat stability and digestive stability. The probability that an introduced protein will become a food allergen is evaluated by applying the criteria given in the assessment scheme and taking all the listed characteristics into account. Although the FAO/WHO scheme recommends the use of animal-based models to assist in predicting potential allergenicity in humans, none are validated for use at this time.

The safety of the remaining edible portion of the food, or of the whole food, is the third key element of the evaluation. Whole foods do not lend themselves to the safety evaluation process that is applied to food additives and other single and defined chemicals found in food. Thus, a detailed comparison is made for the safety of a food derived from a genetically modified plant with the safety of its traditional counterpart food. The evaluation includes comparison of composition and nutritional value as well as comprehensive macro- and micronutrient analyses. Typically, 50 or more different key nutrients and antinutrients are assessed either in raw materials (e.g., grains) or, where appropriate, in food products that are derived from comparable conventional and biotechnology-derived plants grown side by side under identical conditions in order to determine if the two plants are equivalent. Equivalence of composition is taken as evidence that substantive changes did not occur in the plant, and the plant is said to be "substantially equivalent" or "as safe as" its conventional counterpart. Voluntary animal feed performance trials often add confidence to the evaluation. Some foods that have known toxicants may simultaneously produce compounds that are thought to be health protective or health beneficial. Changes in the concentrations of compounds that have potential health significance are evaluated as well.

The first biotechnology-derived crop to enter the market was the FLAVR SAVR tomato, cleared by the FDA in 1994 after approval of a food additive petition for the neomycin phosphotransferase protein encoded by a marker gene that had been introduced into the tomato (FDA 2001b). A food additive petition, however, generally is not required by the FDA, although the FDA has consistently asserted the right to use the petition process for crops that cannot be judged to be substantially equivalent. It should be noted that the use of the food additive petition process for the safety evaluation and approval of whole foods may be scientifically inappropriate (OECD 1993). Whole foods can be evaluated best in comparison with their traditional counterparts. That comparison is the basis of the much-discussed and often misinterpreted principle of Substantial Equivalence (FAO/WHO 2001). The necessity to compare whole foods with their traditional counterparts is the reason the FDA has published guidelines for premarket safety assessment and voluntary premarket consultation for crops that are not materially different from their conventional counterparts. To date, all biotechnology-derived products that have been commercialized since the FLAVR SAVR tomato have been subjected to voluntary premarket review by the FDA. That this process has occurred in the past, however, should not be taken to mean that it will always be followed in the absence of a mandatory process. It has been suggested that the establishment of a mandatory review process would clarify FDA requirements, impose equal rules on all agricultural biotechnology organizations, and provide a framework for a transparent and open regulatory review that would enhance consumer confidence.

The FDA has responded to public comments by proposing a mandatory premarket notification process for all products produced by agricultural biotechnology. The new FDA-proposed regulation would enhance the transparency of the regulatory process and improve the public's access to the data. The proposed FDA regulation, however, does not compel the FDA to publish an explanation of the scientific rationale on which its opinions have been based.

Consistent with FDA policies for foods developed by other methods, labeling of food derived from biotechnology-derived crops is required only when the biotechnology-derived crops differ significantly in composition, nutritional value, or health effects from their conventional counterparts. These differing products, when offered for sale, could not be represented as being equivalent to their conventional counterparts. If the product is approved, labels would be required to declare the compositional differences clearly. All biotechnology-derived products commercialized to date, except two, have been found to be substantially equivalent, and because the FDA has concluded that they are as safe as their conventional counterparts, the FDA does not require these products to be labeled differently from their conventional counterparts. The two exceptions are high-laurate canola and high-oleic-acid soybean products, both of which have oil composition that differs from the conventional counterpart. This difference requires that the common

or usual name be changed to describe the new foods. The FDA has determined that voluntary labeling is permissible and has circulated proposed voluntary labeling guidelines designed to assure that such labeling is truthful and not misleading (FDA 2001c).

Postmarket Surveillance and Stewardship

After regulatory approval and commercial introduction of a new biotechnology-derived plant variety, it may be desirable and/or necessary to test for the presence of a trait(s) introduced using modern biotechnology techniques. Detection and tracking may be required as important components of a quality assurance program. Testing may be required by regulation in importing countries or may be necessary to establish compliance with product specifications set by a buyer (particularly if the product is labeled "biotech-free"). Methods have been developed, therefore, to detect and track biotechnology-derived products after they enter the commodity stream. Identifying the presence of an introduced genetic trait in food, feed, or animal products can be done by looking for the inserted DNA itself, a DNA marker, or the encoded protein that was expressed in the plant based on instructions from the inserted DNA. No single generic test for biotechnology-derived varieties exists because not all inserted traits are alike. Thus, it is necessary to know which bioengineered trait is being sought in order to select the appropriate method prior to testing. It also is important to recognize that testing adds to cost and requires trained personnel.

Identity Preservation: DNA and Protein Detection

Testing for DNA

The most commonly used test for the presence of inserted DNA is the polymerase chain reaction (PCR), a specific and sensitive technique. Either entire genes or short fragments of DNA can be detected using this method. Prior knowledge of the DNA sequence being tested for is necessary because "primers" with a complementary or matching DNA sequence are required in the PCR reaction. Therefore, the PCR method can be used as a screening technique for the presence of selected known sequences present in specific genes or gene fragments. The PCR method is especially good for detecting intact DNA (such as would be present in raw grain) or large fragments of DNA (such as would be present in minimally processed foods). When the goal is to detect a specific sequence of DNA in more highly processed foods, however, the PCR method is more difficult to apply and produces less reliable results. Processing of food can cause breakage of the DNA, and certain food matrices can interfere in the assay or prevent extraction of DNA suitable for assay.

Tools and kits that automate part or all of the PCR protocol are available and have led to greater testing reproducibility among laboratories using equivalent samples. No standardized protocol exists for this test, however, so there can be a large amount of variability in the results reported from different laboratories. Because the PCR method is extremely sensitive, it is critical to avoid unintended contamination of samples, a misstep that can give false positive results. Additionally, because of the high sensitivity of the method, it is very important to use the appropriate controls. Contamination is a major concern in animal products testing.

Testing for Specific Proteins

There are methods available for detecting the presence of a transgenic protein, but these methods are highly specific and can detect only the specific or very closely related transgenic proteins. A method that employs highly specific antibodies that can bind tightly to the transgenic protein is used to detect the presence or determine the amount of the expressed transgenic protein. The high affinity of the antibody for the target protein can be employed in assays designed to detect the protein. One method of this type is called the enzyme-linked immunosorbent assay, or ELISA. The ELISA can be used qualitatively for screening or quantitatively to detect actual amounts of transgenic protein. The ELISA, a very specific and sensitive test, often comes in an easy-to-use kit with all reagents premade and premeasured.

The ELISA methodology was used to create another transgenic protein detection method called the lateral flow strip (LFS). The LFS method is simple and easy to use because it does not require highly skilled personnel or specialized equipment. The LFS is similar to a home pregnancy test kit in that it uses a color change to indicate the presence of the transgenic protein. These strips are most appropriate for evaluating crops that have undergone minimal processing, and they are best used on farms, at grain elevators and other grain-handling enterprises, and by food ingredient suppliers. Some of the LFSs are sensitive enough to detect one kernel of corn that produces a specific protein within 10,000 kernels of corn that do not contain the protein. Care must be taken, however, to ensure that appropriate sampling procedures are followed. As with any method described in this section, personnel must be adequately trained and appropriate comparisons or controls must be selected for meaningful and reliable results to be produced. Without these components, both false positive and false negative results will be obtained and diminish the reliability and predictive value of the test.

It is important to note that the antibodies used in making ELISAs or LFSs for raw products often are not validated for detecting that same protein in processed food products. Certain food processing procedures can destroy the part of the protein recognized by the antibody. The protein still could be present in the food in a largely intact state while a false negative result would be observed. Both denaturation caused by thermal processing or cooking as well as fragmentation caused by mechanical shearing can produce similar false negative results. Therefore, unless appropriate validation has been performed on the antibodies and the correct controls have been used, antibody-based methods should not be used for detection of transgenic protein in processed food products.

A third test for detecting the presence of transgenic proteins is the Western blot method. A more sophisticated technique requiring specialized equipment and training, the Western blot is used primarily in research applications. Whereas the ELISA and LFS methods reveal that an antigen-antibody reaction has occurred, the Western blot technique reveals additional information about the size of the protein or protein fragment that is giving a positive reaction with a specific antibody. Because this method uses antibodies specific for the expressed transgenic protein, the caveats listed previously for antibody validation and controls also apply to this method.

Current methods used for detecting transgenic DNA and protein are appropriate for the agricultural biotechnology-derived crops that have been approved to date. Some limitations exist, however, in using the current methods to detect DNA and transgenic protein in processed food products. In the future, more sophisticated detection methods may be necessary to assist in identity preservation of biotechnology-derived crops or products of biotechnology-derived crops that possess enhanced nutritional or nonfood uses, such as those containing pharmaceuticals or nutraceuticals, or compounds such as biopolymers.

Regulatory Requirements for Postmarket Testing and Surveillance

Some crops, such as Bt corn and Bt cotton, were approved for commercialization with requirements for subsequent testing and surveillance. Although the EPA has approved under FIFRA the use of Bt proteins in several crops, the registrations have been conditional; the companies and growers involved must comply with postmarket requirements for resistance management programs. In theory, the constant expression of Bt protein in biotechnology-derived crop plants could lead to more rapid development of pests that are resistant to that specific Bt protein. The only well-documented cases of Bt resistance in the field reported to date resulted from the use of conventional Bt microbial sprays (Shelton et al. 1993; Tabashnik et al. 1990). The EPA, however, does not require postmarket insect resistance monitoring programs for microbial Bt products. Continued field surveillance will be necessary to monitor whether or not the currently recommended management strategy successfully prevents the development of resistance to Bt crops. The EPA, after consultation with the USDA and outside scientific advisors, placed additional terms and conditions on the registrations for Bt corn and Bt cotton. The EPA required postmarket monitoring for insect resistance and continuing evaluation of new monitoring methods.

The EPA also has used its FIFRA authority to issue data call-ins requiring postmarket studies on the potential effect of Bt corn plants on monarch butterfly populations. This requirement was prompted in response to a published letter that Bt corn pollen could kill monarch butterfly larvae when the larvae fed on high concentrations of Bt pollen-coated milkweed leaves (Losey, Rayor, and Carter 1999). Subsequent studies demonstrated that the exposure of monarchs to Bt corn pollen in natural settings is very low and is unlikely to cause significant mortality (EPA 2001a; Hellmich and Siegfried 2001). These follow-up studies successfully applied a research management paradigm in which representatives from academia, government, nongovernmental organizations, and the crop biotechnology industry worked together to oversee and coordinate the efforts of independent research teams jointly financed by industry and government funds. This cooperative process ensured that the right questions were addressed and that scientifically sound, unbiased data were produced.

Voluntary Product Performance and Safety Tracking

Companies marketing biotechnology plant products have developed voluntary product stewardship programs that have a significant postmarket component. Examples of ongoing crop biotechnology stewardship issues include seed quality and purity, insect resistance management plans for Bt products and other plant-incorporated protectants, outcrossing and open pollination, identity preservation, product channeling, and trade. Publicly and privately funded research organizations in the United States, Europe, and several Pacific Rim countries have conducted studies that have validated the safety of meat, milk, and eggs from animals that consume biotechnology-derived crops (Clark and Ipharraguerre 2001; Faust 2000). Neither introduced DNA nor newly expressed protein(s) from biotechnology-derived crops

has been found in meat, milk, or eggs from animals fed biotechnology-derived crops (FASS 2001).

A consortium of biotechnology companies and associations involved in research, development, and introduction of agricultural biotechnology products formed the Agricultural Biotechnology Stewardship Technical Committee (ABSTC) to meet four product stewardship goals in a coordinated manner. These goals include (1) addressing scientific issues central to responsible stewardship of agricultural ecosystems; (2) developing practical solutions that offer a balanced approach to managing risk; (3) providing broad-based expertise and educational resources; and (4) promoting broad stakeholder involvement and establishing industry practices and standards for product stewardship. For example, the ABSTC addresses several issues involving livestock performance and the composition of animal products, including the potential presence of transgenic proteins and transgenic DNA in livestock that are fed biotechnology-derived crops and the coordination of livestock-related research projects through public and independent research organizations.

Research protocols developed by ABSTC were designed to address common factors that produce erroneous results. These factors include the number of experimental units, selection of appropriate treatments and corresponding controls, consideration of growing conditions for treatment crops, appropriate characterization of treatment and control feedstuffs, and adequate diet formulation. Other efforts of this committee include cooperation with academics, grower associations, and the EPA to implement strengthened insect resistance management plans in the United States and joint funding with the USDA for university research on potential impacts of Bt crops on nontarget organisms.

Summary and Recommendations

The objective of this paper was to describe and evaluate the performance of the regulatory system applied to crops derived through biotechnology in the United States. This paper shows that the U.S. regulatory process for biotechnology is multifaceted and involves several agencies. The answer to the first question posed in the Introduction, "How are safety assessment and regulatory reviews conducted?" constitutes the majority of this paper.

In answer to the second question posed, "Can obvious strengths and weaknesses of that process be identified?" both strengths and weaknesses are identified and described throughout the paper. The authors conclude that the flexible case-by-case approach that has been adopted by regulatory agencies is a strength; there are dissenters who would view it as a weakness. Consequently, there exists considerable difference of opinion on the issue of whether or not the system has served us well. The authors concur with the widely held belief that the introduction and planting of biotechnology-derived crops in the United States has occurred without harm, whereas others suggest that the presence of unapproved StarLink corn in the food supply supports the concern that the system is not perfect and the potential for harm exists. There is general agreement, however, that both the public's access to information and the opportunity for public input into the process can and should be improved. The fact that the FDA premarket review process is voluntary is a potential weakness, even though the products brought to market to date have been reviewed by the FDA. If adopted, the FDA's proposal to make their process mandatory should address that potential weakness.

In response to the third question posed, "Can improvements be made in conduct and direction of independent research, in performance of safety assessments, in opportunities for consumer participation, or in any other aspects of the regulatory process that will both enhance the quality of the assessments and further ensure the ultimate safety of biotechnology-derived crop products?" the authors believe that the answer to this question is always "Yes," because there is no system for which improvements cannot be made. In the case of a new technology such as agricultural biotechnology, there are always as-yet-unanswered research questions, as well as differences in opinion as to what level of safety is "reasonable" and commensurate with established and reasonably foreseeable risks. It is particularly important that the system be flexible, robust, and comprehensive enough to evaluate future products that are not substantially equivalent to their conventional counterparts. The authors offer ten recommendations that they believe will clarify and enhance the regulatory process.

In answer to the final question posed in the introduction, "Are improvements possible that will enhance public confidence in the regulatory process?" the authors caution against changes that are made solely for the purpose of enhancing public confidence. Public confidence is earned best through science-based pursuit of answers to ongoing questions and through proper functioning of the regulatory system. Public confidence also requires meaningful dialogue between the public and those involved in the science. Several of the following recommendations are designed to make the regulatory process more accessible, more transparent, and more inclusive. The authors also propose that the regulatory agencies be more forthcoming in explaining their policies and decisions to consumers.

Recommendations for Regulation

1. Retain the current case-by-case safety assessment approach and continue to emphasize regulatory conditions carefully tailored to address risks identified for individual biotechnology-derived plant products. Agencies must maintain the flexibility to assure that rigorous, science-based safety assessments are conducted for each new product or product category. Agencies should strive to coordinate their activities to form a seamless and consistent regulatory system.

2. Finalize the FDA's current proposal for a mandatory, premarket notification in lieu of the present policy of voluntary consultation for all food products of agricultural biotechnology. The FDA should be commended for proposing a mandatory premarket notification process. The need for and functioning of the mandatory premarket notification policy should be reevaluated in five years. We encourage the FDA to publish the submitted data summaries and to develop a process for publishing a detailed rationale for its decision making at the completion of their process.

3. Provide the public with rapid, comprehensive accessibility to applications and supporting health and safety data submitted to regulatory agencies for biotechnology-derived products. Increased transparency of the regulatory process, particularly at the FDA, could increase opportunities for public input and strengthen consumer confidence in the safety evaluation process. Efforts should be made to determine whether increased access to information and regulatory decision criteria will be sufficient to increase consumer confidence in the regulatory review process and the safety of the food supply in the United States.

4. Issue approvals for both food and feed use for crops that are intended to enter commodity streams. There should be no split approvals for commodity crops, as occurred with StarLink corn. In the future, products intended exclusively for special food, feed, veterinary, medical, or industrial uses may be developed. A robust identity preservation system or some alternative means of channeling the product exclusively to the correct use should be in place prior to the product's approval and commercialization. Before such products are introduced, validated testing methods must be available.

5. Provide the additional resources sorely needed for key regulatory review functions. Resources must be allocated to agency staff and organizational needs, especially at USDA/APHIS, the EPA's Office of Pesticide Programs, the FDA's Center for Food Safety and Applied Nutrition, and the FDA's Center for Veterinary Medicine. These resources should be used for timely scientific review of data submissions and efforts to improve the transparency of the review process. Resources also should be allocated to support greatly expanded outreach and consumer information programs offered by the regulatory agencies.

Recommendations for Research and Development

1. Conduct additional research on selected topics to ensure that present-day questions can be answered and that future developments will be assessed adequately. Additional support for evaluative research could come either from government agency programs, such as the National Research Initiative Biotechnology Risk Assessment Program, from joint government/industry projects, or from consortia of sponsors. Research conducted independently will enhance confidence in the validity of data submitted to government agencies.

2. Develop rapid screening methods for biotechnology-derived crop proteins in raw agricultural commodities, such as grain and vegetables. Routine compliance methodologies need to be improved and made publicly available. Protein detection methods must be rapid, robust, and available for use under actual field conditions. These methods should be standardized, validated, and available prior to market entry of a biotechnology-derived crop.

3. Conduct additional research to support regulatory oversight and product stewardship of biotechnology-derived crops currently on the market. Research topics would include improvements to insect resistance management practices for Bt crops as well as agronomic practices for biotechnology-derived crops that would enhance identity preservation efforts.

4. Carry out additional research on the potential health, safety, and environmental effects of biotechnology-derived products that are not designed to be substantially equivalent to their conventional counterparts (sometimes referred to as next generation biotechnology-derived crops). Such crops would include those having improved competitiveness, enhanced tolerance to stress, or enhanced nutritional value.

5. Conduct additional research on food allergies and identification and characterization of allergenic food proteins. Such research should include the development of representative, reproducible, and validated animal models for identification of probable allergens as well as the determination of the dose and exposure necessary for sensitization and elicitation of food-allergic reactions. A centralized, publicly accessible, searchable database of known allergens should be created and maintained.

GLOSSARY

Antibodies. Proteins that are produced by an organism in response to exposure to foreign substances called antigens. Antigens are most often foreign proteins. Antibodies to an antigen are very specific for that antigen and usually bind very tightly to the antigen. The ability of antibodies to bind strongly and specifically to antigens can be used as the basis for qualitative and quantitative assays (see, for example, **ELISA**).

Bioengineering. The technique of removing, modifying, or adding genes to a chromosome to change the information it contains. By changing this information, genetic engineering changes the type or amount of proteins an organism is capable of making.

Biotechnology. (Dictionary definition) The use of living organisms, living cells, and/or biological molecules to solve problems and make useful products. (Modern definition) The application of the techniques of molecular biology and/or recombinant DNA technology, or in vitro gene transfer, to develop products or impart specific capabilities to organisms.

Bt protein. A protein produced by *Bacillus thuringiensis* that is toxic to a narrow range of insect pests. There are a large number of Bt proteins, each having specificity for a limited number of insects. Genes encoding Bt proteins, sometimes called Cry proteins because they occur as minute crystals in the bacteria that produce them, have been transferred into crop plants to make the crops resistant to specific insect pests.

Digestive stability. The human digestive system breaks proteins down into the individual amino acid building blocks of which they are constructed. Different proteins are broken down by the digestive system at different rates. Proteins that are not readily digested are said to be stable.

Environmental fate. The ultimate chemical form and location of compounds that are released into the environment.

Enzyme-linked immunosorbent assay (ELISA). An immunological assay technique that can be used to qualitatively and quantitatively measure a specific protein.

Event (see also **Transformation**). Biotechnologists refer to the transfer of a gene into a target plant as an event.

Gene. The physical unit of inheritance, made up of a particular sequence of nucleotides found on a particular chromosome. In bacteria, genes also can often be found on small extrachromosomal pieces of DNA called plasmids. Viruses also contain small fragments of DNA (or RNA) that contain genes. Regardless of the source, a specific gene is composed of a sequence of DNA that usually represents the coded description or blueprint for a specific protein.

Gene flow. The concept that in natural ecosystems genes can move within and among plant species, often by cross-pollination.

Identity preservation. A system for keeping a specific crop variety separate from the commodity stream during growth, harvest, transportation, processing, and distribution.

Open-pollinating. A plant that is capable of being pollinated by other individuals of the same or closely related species.

Polymerase chain reaction (PCR). A very sensitive, rapid biochemical assay system for detection of specific sequences of DNA that is often used to indicate the presence or absence of specific genes. PCR can be used to determine whether an organism contains specific DNA sequences. The presence of specific sequences might be an indicator that a plant has been modified through biotechnology.

Protein. A complex biological molecule composed of a chain of amino acids that are assembled in the linear order specified by the gene that encodes the protein (see also **Gene**). Proteins are almost always biologically active only when the chain of amino acids is folded into a specific 3-dimensional conformation. Proteins have many different biological functions; for example, enzymes, antibodies, and hair are proteins.

Transformation (see also **Event**). The process of moving a gene from one organism into another. Transformation is used for the introduction of genes conferring potentially useful traits into plants, microorganisms, livestock, fish, and tree species.

Transparency. Applied to a political process, transparency means that nothing has been hidden from view. Meetings have been announced in advance, hearings have been open to the public, public comments have been collected, and, once deci-

sions have been made, the rationale for the policy adopted is explained clearly.

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