

## US REGULATION OF AGRICULTURAL BIOTECHNOLOGY: AN OVERVIEW

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Three federal agencies—the United States Department of Agriculture (USDA), Environmental Protection Agency (EPA) and Food and Drug Administration (FDA)—share primary responsibility for regulating biotechnology in the United States. This article describes each agency's role as it relates to agricultural biotechnology. The article also mentions some controversies regarding the existing regulations, and pending initiatives to revise them.

*Key words:* agricultural biotechnology; EPA; FDA; law; regulation; USDA.

Agricultural biotechnology has been a source of both public controversy and technological achievement. One major recent controversy was the discovery in taco shells of StarLink™ corn, a genetically engineered corn variety which was approved for animal feed use but not direct human consumption. This discovery caused major food recalls and disruptions in the food distribution system, even though it was not shown that StarLink™ corn actually posed any significant health risks.

While the StarLink™ controversy cast a shadow for the immediate present over agricultural biotechnology, a major scientific breakthrough reminded the world of its immense future potential. In December 2000, an international consortium of scientists announced the complete genetic sequencing of *Arabidopsis thaliana*, the first plant to have its genome fully sequenced. This discovery seems certain to inspire a new wave of research, to understand the functions of newly discovered genes and develop new commercial applications to take advantage of them.

Both the controversies and the promise of new products have focused attention on the United States (US) regulatory structure for biotechnology. At issue is whether the existing regulatory structure is adequate to assure public safety without discouraging innovation. This article presents an overview of current US regulations for agricultural biotechnology. It also discusses some of the concerns, which have been raised about existing regulations, as well as pending federal initiatives to review or revise them.

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## **Overview Of The Regulatory System**

The existing US regulatory framework for biotechnology is based on the Coordinated Framework for Regulation of Biotechnology Products, which was published in the Federal Register on June 26, 1986 (51 Fed. Reg. 23,303). At the time, there was considerable debate as to whether biotechnology regulation would require entirely new laws and a new agency specifically dedicated to its regulation (the debate continues to the present day). The Coordinated Framework rejected that approach. Rather, it reflected a position that biotechnology could be adequately regulated through the existing federal infrastructure and by adapting existing laws to new technologies.

Under the Coordinated Framework, three federal agencies – the US Department of Agriculture (USDA), the US Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) share primary responsibility for regulating biotechnology. The United States Department of Agriculture reviews biotechnology-derived applications, which contain or are produced using potential plant pests. The United States Department of Agriculture also regulates veterinary biologics, which are products derived from living sources, such as blood products and vaccines, and is largely responsible for assuring the safety of meat and poultry products. The Environmental Protection Agency regulates biotechnology-derived plant or microbial pesticides or new chemical substances. The Food and Drug Administration, which regulates the safety of most foods, drugs for human or animal use, biologics for human use, and medical devices, is the lead regulatory agency with respect to these products.

The discussion below summarizes the regulations of each of these agencies as they relate to agricultural biotechnology. The principal emphasis of this paper is on plant biotechnology, although transgenic animals are also increasingly utilized in biotechnology. The discussion focuses first on the USDA, then the EPA and then the FDA, as this represents the order in which a person developing a new agricultural biotechnology product might commonly encounter each of these agencies.

### **Animal And Plant Health Inspection Service**

The USDA Animal and Plant Health Inspection Service (APHIS) is the principal USDA agency involved in biotechnology regulation. The Animal and Plant Health Inspection Service is responsible for protecting US agriculture against threats from pests and diseases.

The Animal and Plant Health Inspection Service regulates field tests and interstate shipments of genetically engineered plants. Under APHIS regulations, most genetically engineered plants are considered “regulated articles.” The Animal and Plant Health Inspection Service must be notified prior to any interstate shipment or field test of these “regulated articles.” In limited cases, described below, a permit must be obtained prior to any field tests or interstate shipments. A person cannot ship a bio-engineered plant freely in interstate commerce until it has been “deregulated” by APHIS. In order to obtain deregulation, the person developing the bio-engineered plant must submit a “petition for deregulation,” discussing the plant’s genetics, potential environmental impacts, and many other factors. If the petition is approved, then the bio-engineered plant is no longer considered a regulated article and may freely be distributed in interstate commerce.

The Federal Plant Protection Act (7 U.S.C. §§ 7701 *et seq.*) is the primary statute under which APHIS regulates agricultural biotechnology. Enacted in 2000, this statute replaced the former Federal Plant Pest Act. Originally intended to prevent the introduction and interstate movement of plant pests, the Plant Pest Act had been adapted by APHIS to regulate genetically engineered plants so that they do not become “plant pests.”

A “regulated article” is defined in APHIS regulations as “any organism which has been altered or produced through genetic engineering” if the donor organism, recipient organism, vector or vector agent is a “plant pest” (7 C.F.R. § 340.1). The Animal and Plant Health Inspection Service defines a plant pest broadly to include “any living stage” of insects, bacteria, fungi, viruses, or various other organisms which can damage or cause injury to plants or plant parts (7 C.F.R. § 340.1). Many plant pathogens commonly used as vectors or promoters in agricultural biotechnology, such as *Agrobacterium* species and cauliflower mosaic viruses, are considered “plant pests” under APHIS regulations (7 C.F.R. § 340.2(a)). Use of any of these “plant pests” to make a transgenic plant makes that plant a “regulated article.” The Agency may also designate as a regulated article any product of genetic engineering which the Agency determines or has reason to believe is a plant pest (7 C.F.R. § 340.1).

The Animal and Plant Health Inspection Service initially required a permit as a pre-condition for any field test or interstate shipment of a regulated article. However, the Agency modified its requirements in 1997, so that the vast majority of new plant releases now require only a notification to the Agency.

Six criteria determine whether a species is eligible for notification. These criteria are as follows:

- The species may neither be a noxious weed under USDA regulations nor considered by the Agency to be a weed in the area where it will be released.
- The introduced genetic material must be stably integrated into the plant genome.
- The function of the introduced genetic material must be known, and its expression in the regulated article must not cause plant disease.
- The introduced genetic material must not cause production of an infectious entity, encode substances known or likely to be toxic to non-target organisms, which are likely to feed or live on the plant species, or encode products intended for pharmaceutical use.
- The introduced genetic sequences derived from plant viruses must not pose a significant risk of creating new plant viruses.
- The plant must not have been modified to contain genetic material derived from human or animal pathogens (7 C.F.R. § 340.3(b)).

A person wishing either to conduct a field test or engage in interstate shipments involving regulated articles must submit a notification to APHIS. After receiving the notification, the Agency responds with either an acknowledgement or denial within 10 days after receiving an interstate movement letter or within 30 days after receiving a notification of an environmental release (7 C.F.R. § 340.3(d)). As of December 6, 2000, APHIS had received over 5,700 notifications, of which over 5,300 had been acknowledged and only 254 had been denied (National Biological Impact Assessment Program [NBIAP], 2000). Agency acknowledgements are valid for one year, and may be renewed by submitting additional notification. The tester must submit a report within six months after termination of the field test and must notify the Agency of unusual occurrences during the test (7 C.F.R. § 340.3(d)). The Animal and Plant Health Inspection Service typically inspects about 10% of the on-going field trials in any given year.

Before the transgenic product may be freely transported and commercialized, APHIS must “deregulate” it. The product sponsor first must petition APHIS for a “determination of non-regulated

status.” This application must include, among other information, details about plant genetics, the nature and origin of the genetic material used, field test reports and effects on other plants (7 C.F.R. § 340.6(c)). The length of time required to obtain the information to support a petition varies, but typically represents two to three years of field test results (and, perhaps, five to ten generations of plants). Researchers often conduct off-season greenhouse testing in order to expedite data collection.

The Animal and Plant Health Inspection Service must respond to a petition within 180 days, which includes a period for public comment. Among the items which APHIS examines in its review of the petition are environmental impacts, including the potential of the plant to cross-pollinate with other plants and potential effect of such cross-pollination; the effect of the plant on wildlife; and the potential of the bio-engineered plant to become a weed or plant pest. Once APHIS has deregulated an article, neither the product nor its offspring require further APHIS review for movement or release within the United States. As of December 2000, APHIS had received 75 deregulation petitions. It had approved 52, while 19 had been withdrawn. None had been formally rejected (NBIAP, 2000) although some applications may have been withdrawn to avoid formal rejection.

One exception to the notification process described above is for plants which have been genetically modified to produce pharmaceutical products (40 C.F.R. § 340.3(b)(4)(iii)). These plants require a permit before field-testing or interstate shipment. Animal and Plant Health Inspection Service policy is to inspect all field trials involving such organisms at least annually, and the Agency has stated that such organisms are not eligible for “deregulation” (White, 2000). In other words, the intent of APHIS is that plants, which have been engineered to produce pharmaceuticals, will remain directly subject to its regulation.

One potential limitation of the APHIS regulations is that they apply only to “plant pests.” At present, most gene transformations utilize one or more designated “plant pests” as either promoters or vectors, so the resulting transgenic plants become subject to APHIS authority. It is possible, however, to perform a gene transformation without using any “plant pest,” in which case APHIS regulations arguably might not apply.

The Animal and Plant Health Inspection Service takes the position that it can designate an entire plant as a regulated article, even if it was not developed using plant pests, if the plant is the product of genetic engineering and the agency determines or has reason to believe it is a plant pest (Council on Environmental Quality and Office of Science and Technological Policy [CEQ/OSTP], 2001). Given this position, APHIS would probably challenge any attempt to introduce a genetically engineered plant into commerce unless the developer of the plant had first gone through the APHIS regulatory review process.

In addition to APHIS, other agencies within USDA are assuming a more active role in regulating biotechnology. Responding to growing pressure from farmers, industry groups, and consumers for clear and predictable guidelines for biotechnology-derived products, the USDA Grain Inspection Packers and Stockyards Administration (GIPSA) recently issued an Advance Notice of Proposed Rule-Making (ANPR) inviting public comments “on how USDA can best facilitate the marketing of grain [and other agricultural products] in a market that includes both crops derived from biotechnology and other crops” (65 Fed. Reg. 71,272 *et seq.* (2000)). An ANPR is an announcement by an agency in the Federal Register that it is contemplating new regulations and inviting public comment. Among the issues on which USDA is seeking comments are whether to develop standards or definitions for what constitutes a biotechnology or non-biotechnology crop, and whether the USDA should provide certifications or analytical detection services for biotechnology products. The United States Department of Agriculture opened a new biotechnology accreditation laboratory in Kansas City, Missouri in November 2000 to help standardize identification of biotechnology-derived

grains. The United States Department of Agriculture has also established an Advisory Committee on Agricultural Biotechnology, composed of representatives of industry, farm groups, academia, and environmental and consumer organizations to assist it in developing biotechnology policies.

## **Environmental Protection Agency**

The Environmental Protection Agency's authority to regulate biotechnology is derived primarily from three federal statutes: the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA); the Federal Food, Drug, and Cosmetic Act (FFDCA); and the Toxic Substances and Control Act (TSCA). Each statute and its implications for the regulation of biotech foods is discussed next.

### Federal Insecticide, Fungicide and Rodenticide Act , 7 U.S.C. §§ 136 *et seq.*

The Federal Insecticide, Fungicide and Rodenticide Act regulates the use of pesticides in the United States. The Environmental Protection Agency has utilized this statute to require registration of pesticides, which have been genetically introduced into plants, and which the Agency refers to as "plant-pesticides." The most economically significant of these plant-pesticides are "Bt crops" (i.e., plants which have been genetically engineered to produce naturally occurring toxins derived from the bacterial species *Bacillus thuringiensis* (Bt)).

The Federal Insecticide, Fungicide and Rodenticide Act defines a pesticide as "any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pests [or] intended for use as a plant regulator, defoliant, or desiccant" (7 U.S.C. § 136u). Under FIFRA, new pesticides must be registered with the EPA before they can be commercially marketed. The Federal Insecticide, Fungicide and Rodenticide Act establishes a balance between benefits and risks. In order to obtain registration, a new pesticide must not cause "unreasonable adverse effects on the environment" (7 U.S.C. § 136a(c)(5)). "Unreasonable adverse effects on the environment" are defined as "(1) any unreasonable risk to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide, or (2) a human dietary risk from residues that result from a use of a pesticide in or on any food" unless the EPA determines that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue" (7 U.S.C. § 136(bb); 21 U.S.C. § 346a).

A party seeking to register a new pesticide under FIFRA must provide evidence of the product's effectiveness, as well as a broad range of data relating to product chemistry, toxicology, environmental fate, and effect on non-target species. Pesticides are among the most tightly regulated products in the United States, after pharmaceuticals. Each use of a pesticide must be registered using the above balancing standard. Prior to applying for registration, applicants may apply for an "experimental use permit" (EUP) in order to conduct field trials. Such field trials are often necessary to obtain the information needed to support registration. Field trials affecting less than 10 acres of land or one acre of water may be exempt from the requirement to obtain a experimental use permit.

With respect to plants, which have been genetically engineered to produce their own pesticides, the EPA developed a policy statement and proposed regulations in 1994 to regulate "plant-pesticides" (59 Fed. Reg. 60,496 *et seq.*). The Environmental Protection Agency does not regulate the entire bio-engineered plant as a pesticide. Rather, it regulates only the "plant-pesticide," which the Agency considers to consist of the pesticidal substance(s) and the genetic material necessary for the production of that substance (61 Fed. Reg. 37,891 *et seq.* (1996)).

As of July 1999, the EPA had approved nine separate Bt toxins for use in potato, corn, and cotton. Most of these registrations are conditional, and expire in 2001 (Environmental Protection Agency

Office of Pesticide Programs Biopesticides and Pollution Prevention Division [EPA/OPPBP], 2000). The Environmental Protection Agency generally has required the planting of non-Bt “refuges” as a condition for registration of a Bt crop. As a condition for purchasing Bt seeds, farmers are required to agree to plant a specified acreage or “refuge” (typically about 20% of the total acreage of the particular crop) of non-Bt crops alongside the Bt acreage. The objective of refuges is to discourage insects from developing resistance to Bt, by providing a safe haven for non-resistant insects, which then can survive and breed with any resistant individuals, which develop.

The Environmental Protection Agency held a meeting of its Scientific Advisory Panel (SAP) in October 2000 to discuss re-registration of Bt crops. The Environmental Protection Agency has taken the position that the Bt crops approved to date have not caused either environmental damages or problems with insect resistance, and recently stated that “[a]vailable data indicate that after five years of commercialization, no reported insect resistance has occurred to the Bt toxins expressed either in Bt potato, Bt corn or Bt cotton products” (EPA/OPPBP, 2000). The Agency stated further that “there are no unreasonable adverse effects from [Bt] products” and that “[g]ene flow to wild species through out-crossing is not a concern for any of the registered Bt plant-pesticides.”

In July 2001, EPA published final rules for regulating plant-pesticides (66 FR 37771 *et seq.* (2001)). The new rules largely codified the Agency's existing practices for regulating plant-pesticides. In response to widespread objections from scientists to use of the term “plant-pesticides,” the new regulations renamed pesticidal substances which had been genetically engineered into plants as “plant-incorporated protectants.” The new rules become effective on September 17, 2001, and are codified at 40 C.F.R. Parts 152 and 174.

#### Federal Food Drug and Cosmetic Act (FFDCA), 21 U.S.C. §§ 301 *et seq.*

Although the FDA is the primary regulatory agency responsible for enforcing the FFDCA, the EPA is responsible for regulating pesticide residues in processed foods and raw agricultural commodities under sections 408 and 409 of FFDCA (21 U.S.C. §§ 346a and 348). When the EPA approves a pesticide for use on agricultural food products, it must either establish a tolerance for that pesticide chemical residue (i.e., an allowable concentration of the pesticide in the food or commodity) or provide an exemption from the requirement for a tolerance. Section 402(a)(2)(b) of the FFDCA deems a food to be adulterated (i.e., illegal) if it bears or contains a pesticide chemical residue at or beyond the level of a tolerance established by the EPA (21 U.S.C. § 342(a)(2)(B); 21 U.S.C. § 346a). The Environmental Protection Agency has granted exemptions from the tolerance requirements for Bt toxins registered as pesticides.

#### Toxic Substances Control Act (TSCA), 15 U.S.C. §§ 2601 *et seq.*

The Toxic Substances Control Act is a “catch-all” statute under which the EPA regulates chemical substances, which are not regulated as drugs or pesticides under other statutes. The definition of a “chemical substance” is very broad and includes any “organic or inorganic substances of a particular molecular identity” (15 U.S.C. § 2602(2)).

Under TSCA, a party seeking to market a “new chemical substance” must submit a pre-manufacture notification at least 90 days prior to initiating such manufacture (15 USC § 2604(a)). New chemical substances are substances, which are not listed on the EPA's Toxic Substances Control Act Chemical Substance Inventory (this inventory presently contains approximately 75,000 chemical substances (Environmental Protection Agency, Office of Pollution Prevention and Toxics [EPA/OPPT], 2001)). This pre-manufacture notification must include test data and information regarding the manufacture, processing, use, intended commercial distribution, and environmental and health effects of the new

chemical. If the EPA does not act within this 90-day period the submitter may begin commercial production of the chemical.

The Environmental Protection Agency has utilized the Toxic Substances Control Act as its legal authority to promulgate regulations for genetically engineered microorganisms (40 C.F.R. Part 725). The Toxic Substances Control Act also might provide a legal basis for the EPA to regulate transgenic plants which produce industrial enzymes or other industrial chemicals, which are neither pharmaceuticals or pesticides. However, TSCA's pre-manufacture notification requirements only apply to new chemical substances or significant new uses of existing substances. Thus, if plants are used to produce industrial products which are already listed on EPA's TSCA inventory, it is not clear whether these products would be subject to TSCA pre-manufacturing notice requirements.

Similar to the USDA, the EPA has taken the position that it can regulate an entire genetically engineered plant as a "chemical substance" under TSCA (CEQ/OSTP, 2001). The Environmental Protection Agency's interpretation is plausible, since the term "chemical substance" is sufficiently broad that it could encompass genetically engineered plants. On the other hand, it seems safe to say that Congress was not thinking of genetically engineered plants when it enacted TSCA in 1976. The Environmental Protection Agency's use of TSCA to regulate bio-engineered plants as "chemical substances" is one example of how federal agencies are attempting to adapt pre-existing laws to regulate new technologies in ways that could not have been foreseen when the laws were first enacted.

### **Food And Drug Administration**

The FFDCFA is the nation's principal statute for regulating the safety of the nation's food and drug supplies. The Food and Drug Administration is the primary agency charged with enforcing this statute. In addition, the Food and Drug Administration regulates certain products in part through its authority under other statutes. For example, the Food and Drug Administration's legal authority to regulate biologics is derived from the Public Health Service Act (42 U.S.C. §§ 201 *et seq.*), although many biologics now are regulated as both drugs under the FFDCFA and as biologics.

The Food and Drug Administration is divided into five centers which respectively regulate (1) food, (2) drugs, (3) biologics, (4) medical devices, and (5) animal drugs. The centers have multiple responsibilities: for example, the Food and Drug Administration's Center for Food Safety and Applied Nutrition (CFSAN) regulates food and color additives, dietary supplements, and cosmetics. The Center for Food Safety and Applied Nutrition has played the largest role in developing the Food and Drug Administration's policies toward regulation of genetically engineered foods. Other FDA centers have played a major role in regulating pharmaceutical products of biotechnology. As products of agricultural biotechnology become more diverse, with therapeutic or diagnostic proteins being produced on plants, and transgenic technologies being used to produce fast-growing animals, the other centers are becoming increasingly involved in the regulation of agricultural and food biotechnology.

As a general rule, whole foods (i.e., fruits, grains, and vegetables) and most "conventional" foods can be placed on the market without pre-approval by the Food and Drug Administration. The Food and Drug Administration's primary legal authority for regulating the safety of such foods is section 402 of the FFDCFA, relating to "adulteration" (21 U.S.C. § 342). The Food and Drug Administration may go to court to "seize" adulterated foods, or take other actions such as requesting a recall when food products pose a risk to public safety (*see, e.g.*, 21 U.S.C. 334).

The second provision central to the Food and Drug Administration's food biotechnology policy is FFDCFA section 403, relating to "Misbranded Foods" (21 U.S.C. § 343). A food is misbranded if its labeling is false or misleading, or if it fails to comply with any of more than 20 other provisions in section 403. Labeling may be considered misleading if it fails to reveal material facts in light of the representations which are made with respect to a product (21 U.S.C. § 321(n)).

The Food and Drug Administration's third key provision for regulating foods is section 409 of the FFDCFA, relating to "Food Additives." A food additive is "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food," unless that substance is "generally recognized as safe" (GRAS) (21 U.S.C. § 321(s)). Food additives include substances which are added to food intentionally, as well as materials such as packaging, which migrate into food in trace amounts during storage or handling. Food additives must be approved by the Food and Drug Administration prior to their use in food, a process that can be time-consuming and expensive.

In 1992, the Food and Drug Administration announced its policy for regulating bio-engineered foods (57 Fed. Reg. 22,984). The Food and Drug Administration took the position that bio-engineered foods should not receive special regulation solely based on the fact that they were produced through genetic engineering. Rather, the Agency would look at the objective characteristics of the food or its components.

The Food and Drug Administration stated further that it would not require special labeling of genetically engineered foods unless the composition of the food differed significantly from its conventional counterpart. For example, if the genetically engineered food contained a significantly different nutritional profile than its conventional counterpart, labeling to that effect might be required. Similarly, a food containing a transgenic protein derived from a source which commonly causes allergic reactions (i.e., milk, tree nuts, legumes, and so on) also could require labeling, unless the product developer could demonstrate that the transferred protein was not itself an allergen. In fact, if a protein which commonly caused allergic reactions were introduced into a food, the Food and Drug Administration might conclude that labeling does not provide sufficient protection and the agency might attempt to stop the product from being marketed.

The Food and Drug Administration's 1992 policy did not require companies to submit their products for review to the Food and Drug Administration prior to marketing. The Food and Drug Administration has stated that "substances intentionally added to food via biotechnology to date have been well-characterized proteins and fats, and are functionally very similar to other proteins and fats that are commonly and safely consumed in the diet and thus are presumptively GRAS" and, therefore, not subject to pre-market review as food additives (Levitt, 2000a). The Food and Drug Administration does, however, encourage developers of bio-engineered foods to voluntarily consult with it on safety and regulatory issues. In this voluntary consultation process, the Food and Drug Administration requests that firms provide a summary of their food (or feed) safety and nutritional assessment to the agency and discuss these results with Food and Drug Administration scientists prior to beginning commercial distribution. The Food and Drug Administration scientists will review this material to verify that safety concerns have been addressed. Specifically, they are concerned that the bio-engineered food contains no new allergens, no increased levels of natural toxicants, and no reduction of important nutrients (Levitt, 2000b). FDA has published a guidance document describing its consultation procedures on the Internet (Food and Drug Administration Center for Food Safety and Applied Nutrition [FDA, CFSAN], 1997).

The Food and Drug Administration does not evaluate the safety of transgenic plant-pesticides, such as Bt toxins or the genetic material responsible for their production. This is considered to be the EPA's

responsibility under FIFRA (see above). Some questions have been raised as to whether dividing the safety review of bio-engineered crops among two agencies is preferable to placing the sole responsibility within a single agency.

Proponents of the FDA biotechnology policy claim that the policy has been a success. All parties who have marketed bio-engineered foods are believed to have voluntarily consulted with the FDA prior to beginning marketing, and there have been no confirmed cases of human health problems directly caused by a commercially marketed genetically engineered food. Critics of the voluntary consultation policy argue that this informal process does not create a public record for the general public to review, and since the process is voluntary, a company could elect to avoid Food and Drug Administration consultation. There are, however, strong commercial pressures for a developer of a bio-engineered food to go through the Food and Drug Administration's process, including increased market acceptance as well as increased protection against potential future legal liability.

In September 2000, a federal court dismissed a challenge to FDA's 1992 policy on genetically engineered foods, which had been filed by a coalition of public interest and environmental groups. The court upheld the FDA's position that genetically engineered foods do not require premarket review, approval of a food additive petition, or special labeling based on the process used to develop them. On January 18, 2001, the FDA published a proposed rule to replace the current voluntary consultations with mandatory premarket consultations (66 Fed. Reg. 4,706 *et seq.*). The Agency also published draft labeling guidance to assist manufacturers who wish to label their foods as either containing or not containing genetically modified ingredients (66 Fed. Reg. 4,839 *et seq.*).

The Food and Drug Administration's proposed new regulations would require developers of bioengineered foods and animal feeds to provide a "premarket biotechnology notice" to the FDA at least 120 days prior to marketing such products. The information required in the notice generally would be similar to that provided in present consultations. However, the information submitted would be publicly available, although there would be opportunities for submitters to request that certain information (or even the fact of the consultation itself) be designated as confidential business information. Within 120 days of the filing of the premarket biotechnology notice, the FDA would respond with a letter describing its conclusion about the regulatory status of the food or animal feed.

Since companies typically notify the Food and Drug Administration at least two years prior to marketing bio-engineered foods, the switch from voluntary to mandatory consultations should not dramatically impact current industry practices. However, the switch to mandatory consultations could help to address a perception that Food and Drug Administration controls are inadequate. In addition, by making most information contained in submissions publicly available, the proposed Food and Drug Administration regulations could help to address the criticism that the present system lacks public transparency. However, some critics have argued that the proposed regulations still lack sufficient transparency, and that the Food and Drug Administration should allow outside third parties an opportunity for public comment during the consultation period.

In March 2001, the Food and Drug Administration modified its Internet site to make the results of its prior consultations publicly accessible (FDA, CFSAN, 2001). Such information had previously been available only through a Freedom of Information Act request. Like the proposed new regulations, the revised web site suggests that FDA is looking for ways to increase the transparency of its regulatory process.

While CFSAN has played the most active role within the Food and Drug Administration in regulating agricultural biotechnology, the other Food and Drug Administration centers are playing an increased role as the range of products continues to diversify. The Food and Drug Administration's Center for

Veterinary Medicine (CVM) was the primary center responsible for approving recombinant bovine somatotropin (rBST), a growth hormone injected into dairy cows. The Center for Veterinary Medicine considered the additions of rBST (or the genetic modifications involved in producing rBST) to constitute the addition of an animal drug, making the product subject to its pre-market approval authority. The Center for Veterinary Medicine is also the lead center in reviewing biotech salmon, which have been genetically engineered to achieve faster and larger growth than traditional salmon.

In addition to food biotechnology, several companies are attempting to produce therapeutic proteins on transgenic plants. Producing therapeutic proteins on plants could offer major cost advantages over traditional production methods, which usually require construction of expensive bioreactor facilities. Transgenic animals are also increasingly being used to produce therapeutic proteins. As a result, the FDA's Center for Biologics Evaluation and Research (CBER), which regulates these products, is assuming a growing role in agricultural biotechnology regulation.

Unlike traditional pharmaceuticals, biologics tend to be complex mixtures with hard-to-define chemical structures. Because it may be difficult to evaluate a defined chemical entity, the Food and Drug Administration's regulatory structure for biologics looks closely at the manufacturing process used to produce them. The Center for Biologics Evaluation and Research has identified a number of unique issues it will have to address in developing regulations for plant-derived biologics. Among these are maintaining the viability and composition of seed stocks, and potential issues regarding heavy metals or other soil contamination at the production site. In addition, the Center for Biologics Evaluation and Research is exploring whether transgenic plants should carry visible distinguishing markers, such as distinguishing colors, so that they can be identified and not intermixed with other plants of the same species. There is also on-going discussion within the Food and Drug Administration on whether pharmaceutical-producing plants will have to be evaluated for food safety (in addition to satisfying human drug or biologic approval requirements) unless the developer can demonstrate that it can completely exclude such products from the food distribution system. The Center for Biologics Evaluation and Research has developed a guidance document relating to the production of therapeutic proteins in transgenic animals, entitled "Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals" (FDA, CFSAN, 1995). The recently published CEQ/OSTP case studies indicated that the FDA and USDA are planning to issue a joint draft guidance document on the regulation of transgenic animals (CEQ/OSTP, 2001).

### **National Environmental Policy Act (NEPA)**

The National Environmental Policy Act (42 U.S.C. §§ 4332 *et seq.*) deserves brief mention because it may become increasingly important as products of agricultural biotechnology become more complex. Enacted in 1969 in response to the environmental movement of the late 1960's, NEPA requires federal agencies to consider the environmental impacts of proposed major federal actions, which could significantly affect the environment. If it appears that a proposed action could significantly affect the environment, then the applicable agency must first prepare an "environmental assessment" which assesses the potential effect of the action on the environment (40 C.F.R. §§ 1501.3; 1508.9). An environmental assessment is not necessary if the agency elects to prepare an environmental impact statement (40 C.F.R. § 1501.3(a)).

If the environmental assessment indicates that the proposed action could significantly affect the environment, then the agency must prepare a more comprehensive "environmental impact statement" (40 C.F.R. § 1501.4). The environmental impact statement must examine the likely effects of the project in more detail and identify potential alternatives to the project. The National Environmental Policy Act requires that environmental impacts be evaluated early in the planning process, rather than

as a mere “after-the-fact” attempt to rationalize the decision (40 C.F.R. §§ 1501.2; 1502.5). The environmental impact statement process frequently results in modifications to the original project to mitigate likely adverse environmental impacts.

Like other federal agencies, both the Animal and Plant Health Inspection Services and the Food and Drug Administration have developed regulations for complying with NEPA (7 C.F.R. Part 372; 21 C.F.R. Part 25). The Animal and Plant Health Inspection Services regularly prepares an environmental assessment when it evaluates a deregulation petition. The Food and Drug Administration also normally prepares an environmental assessment when it approves a new drug. Both agencies have regulations for implementing NEPA requirements. In many cases, the private sector applicant will contribute significantly to preparation of the environmental assessment. To date, APHIS has not required an environmental impact statement for a deregulation petition, and the FDA has not rejected a new drug application solely for NEPA-related reasons. Since the EPA's regulatory reviews generally focus primarily on environmental impacts, the Agency often has been considered exempt from the requirement to prepare a formal environmental assessment or impact statement.

### **CEQ/OSTP Biotechnology Assessment Process**

The White House Council on Environmental Quality (CEQ) and the Office of Scientific Policy (OSTP) completed a comprehensive interagency review of environmental regulations pertaining to agricultural biotechnology in January 2001 (CEQ/OSTP, 2001). Representatives from the EPA, FDA, APHIS, and other federal agencies participated in this review. The end product of this review was a series of case studies examining how the current regulatory regime would handle six different classes of biotechnology products including (1) growth enhanced salmon; (2) Bt corn; (3) herbicide-tolerant soybeans; (4) farm animals producing human drugs or biologics; (5) hybrid poplar trees used for bioremediation; and (6) bacteria used for bioremediation and biosensing. The case studies also included several “sidebars” which evaluated variations on each of these six products, such as pharmaceutical-producing plants. The interagency assessment was also originally intended to develop conclusions and recommendations regarding the strengths and weaknesses of the current system, but the various agencies involved were unable to reach agreement on these issues within the applicable time frame. Despite this omission, the case studies offer a detailed and practical perspective on how the US biotechnology regulatory system presently functions. Of note, CEQ and OSTP stated in their introduction to the case studies that “no significant negative environmental impacts have been associated with the use of any previously approved biotechnology product” (CEQ/OSTP, 2001).

### **Conclusion**

United States regulation of agricultural biotechnology is in a state of flux. While there is no clear evidence that existing bio-engineered plants pose any measurable health or environmental threat, significant public concerns remain regarding the safety and environmental impacts of agricultural biotechnology. Furthermore, new products are in development, which may present regulatory challenges quite different from the products approved to date. Several new regulatory initiatives are pending, and it remains unclear whether existing laws will prove sufficient to regulate rapidly evolving new technologies. If the immense potential of agricultural biotechnology is to be realized, then it will be necessary to establish a regulatory scheme which addresses public concerns while encouraging innovation.

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