Pew Initiative on Food and Biotechnology

Guide to U.S. Regulation of Genetically Modified Food and Agricultural Biotechnology Products

Executive Summary

The products of biotechnology[1] are regulated under the same U.S. laws that govern the health, safety, efficacy, and environmental impacts of similar products derived by more traditional methods. The federal policy that no new laws were needed to regulate the products of biotechnology was first adopted in 1986 by the federal regulatory agencies in the Coordinated Framework for Regulation of Biotechnology. The policy was based on the assumption that the process of biotechnology itself posed no unique or special risks. Further, this policy stated that a commercial product, regardless of its manner of production, should be regulated based on the product's composition and its intended use. In other words, foods developed via biotechnology would be regulated in the same way as other foods developed through conventional processes. Likewise, microbial pesticides developed from biotechnology would be regulated in the same manner as other microbial pesticides.

As a result, no single statute and no single federal agency govern the regulation of biotechnology products. The products of biotechnology span a wide range of foods, drugs, and chemicals, and are thus governed by a complex range of laws that apply to all foods, drugs and chemicals. Under these laws, three federal agencies – the Food and Drug Administration, the Department of Agriculture, and the Environmental Protection Agency – have primary responsibility for the regulation of biotechnology products. At least ten different laws and numerous agency regulations and guidelines cover such products as food, animal feed, human and animal drugs and biologics, pesticides, plant pests, and toxic substances. Each of these laws was developed before the advent of biotechnology products and reflects widely different regulatory approaches and procedures.

As the technology has advanced, fitting biotechnology products into precise product categories has become more difficult; federal regulatory agencies have responded with additional regulations and guidance specific to particular biotechnology products. For example, the development of crop plants that were genetically modified to make their own pesticide presented the regulatory agencies with a product that was simultaneously a potential plant pest, a food, and a pesticide. The novelty of a plant making its own pesticide through genetic engineering led EPA to develop new regulations specifically applicable to "plant-incorporated protectants." Thus, while there are no laws specific to

[1] For the purposes of this paper, the term "biotechnology" refers to the use of recombinant DNA technology to transfer genetic material from one organism to another.

biotechnology products, agencies have developed a number of regulations and guidelines that address the application of existing laws to biotechnology products.[2]

Laws and regulations may apply to the genetically modified plant, animal or microorganism itself, such as in the case where a genetically modified crop is used for animal feed or human food. In addition, however, in some cases a genetically modified plant, animal, or microorganism creates a further product that itself can also fall under federal regulations. For example, an animal could be genetically engineered to make a protein in its milk that can be extracted to create a medical drug or diagnostic. A food plant could be altered to make proteins that could be extracted to make industrial chemicals. In such cases, both the genetically engineered organism and its products could be the subject of regulatory review.

This report is intended to provide a general descriptive guide to the current set of U.S. laws and regulations under which products of biotechnology are reviewed for health, safety, efficacy, or environmental impacts. It focuses primarily on agricultural biotechnology, defined for the purpose of the report to mean the use of rDNA techniques to modify plants and animals traditionally used as food or fiber sources. Therefore, the report does not address regulations of biomedical applications of rDNA technology using microbial organisms or laboratory animals. Nor does the report discuss in any detail the governance of biotechnology research funded by the federal government.

The report describes the legal authority and the agency review "pathways" as published in agency procedures and regulations. The report does not, however, attempt to evaluate the adequacy, efficacy, or efficiency of the current regulatory system, or to evaluate the agencies' performances under these laws and regulations, issues which are the subject of continuing public debate.

Agencies. Regulation of biotechnology products currently falls primarily under the jurisdiction of three regulatory agencies: the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and the Environmental Protection Agency (EPA).

- FDA has responsibility for the safety of food and animal feed, and for the safety and efficacy of human drugs and biologics, and animal drugs.[3] Within the FDA, there are four centers with responsibilities for biotechnology products: the Center for Food Safety and Applied Nutrition (CFSAN); the Center for Veterinary Medicine (CVM); the Center for

[2] Statutes (laws) are enacted by the U.S. Congress, under which federal regulatory agencies are given authority to carry out broad prohibitions or restrictions established by the statute. The agencies issue regulations to implement the laws by establishing more specific requirements and restrictions. Policy guidance documents are not legally binding, as are statutes and regulations; they provide an agency's viewpoint on how it intends to implement certain regulations and offer advice on how best to comply with those regulations.

[3] FDA also has responsibility for regulating medical diagnostics and devices, which are outside the scope of this paper.

Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER).

- EPA has responsibility for the use of pesticides and setting allowable levels (tolerances) of pesticide residues in food, and for the regulation of non-pesticidal toxic substances, including microorganisms.
- USDA has responsibility for the safety of meat, poultry and egg products; for regulating potential agricultural plant pests and noxious weeds; and for the safety and efficacy of animal biologics. Within USDA, the Animal and Plant Health Inspection Service (APHIS) has the major responsibility for biotechnology regulation, with additional possible responsibilities for the Food Safety and Inspection Service (FSIS).

Laws. The major statutes under which the above agencies have been given regulatory or review authority include the following

- The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) (EPA);
- The Toxic Substances Control Act (TSCA) (EPA);
- The Food, Drug and Cosmetics Act (FFDCA) (FDA and EPA);
- The Plant Protection Act (PPA) (USDA);
- The Virus Serum Toxin Act (VSTA) (USDA);
- The Public Health Service Act (PHSA)(FDA);
- The Dietary Supplement Health and Education Act (DSHEA) (FDA)
- The Meat Inspection Act (MIA)(USDA);
- The Poultry Products Inspection Act (PPIA) (USDA);
- The Egg Products Inspection Act (EPIA) (USDA); and
- The National Environmental Protection Act (NEPA).

SUMMARY CHARTS

Chart 1. Regulation of Genetically Modified Organisms

Genetically Modified Products	Agency	Law
Plants		
Plant Pests	USDA-APHIS	PPA
Plant-Incorporated Protectants	EPA	FIFRA
Plants producing toxic substances	EPA	TSCA
Animals		
Animals	FDA	FFDCA
Animals producing toxic substances	EPA	TSCA
Microorganisms		
Microorganisms	EPA	TSCA
Microorganisms if plant pest	USDA-APHIS	PPA

Chart 2. Regulation of Products Derived from Genetically Modified Organisms

Genetically Modified Product	Agency	Law
Human Food		
Whole Food		
Plants (*i.e.*, vegetables, fruits)	FDA – CFSAN	FFDCA
Meat, Poultry and Eggs	USDA – FSIS	MIA; PPIA; EPIA
Food Articles		
Food Additives	FDA – CFSAN	FFDCA
Dietary Supplements	FDA - CFSAN	DSHEA
Animal Feed	FDA - CVM	FFDCA
Drugs and Biologics		
Human Drugs	FDA - CDER	FFDCA
Human Biologics	FDA - CBER	PHSA
Animal Drugs	FDA – CVM	FFDCA
Animal Biologics	USDA – APHIS	VSTA
High Value Products		
Cosmetics	FDA - CFSAN	FFDCA
Pesticides	EPA	FIFRA
Other substances if toxic	EPA	TSCA

Acknowledgements

The Pew Initiative on Food and Biotechnology gratefully acknowledges the significant contributions of Andrew C. Fish, Esq., FoxKiser, and Dr. Larisa Rudenko, Integrative Biostrategies, primary authors of this report.

GUIDE TO U.S. REGULATION OF AGRICULTURAL BIOTECHNOLOGY PRODUCTS

September 2001

I. INTRODUCTION

The current debate over biotechnology raises complex policy questions about the appropriate use and regulation of a technology that has begun to alter the way we produce food and manufacture a wide range of industrial products. Critics have raised concerns about food safety, environmental risks, and ethical issues associated with the technology, while supporters have pointed to a range of potential benefits, including reduced pesticide use and more nutritious foods.

To help the public and policymakers get a better understanding of agricultural biotechnology issues, the Pew Initiative on Food and Biotechnology prepared this paper to provide an overview of the way the United States currently regulates agricultural biotechnology products. In the past few decades, scientists have used recombinant DNA (rDNA)[1] techniques to introduce genetic constructs (*i.e.*, genes of interest plus other important DNA sequences required for the transfer of the genes or their expression in the host organism) into the genomes of plants and animals to create "transgenic" organisms that have new traits. For the purposes of this paper, the term "agricultural biotechnology" refers to the use of rDNA techniques to modify crops and animals traditionally used as food or fiber sources. The focus of the paper is on foods derived from plants and animals, but the production and regulation of other products made from transgenic plants and animals, such as drugs and industrial chemicals, are also discussed. The report does not address regulations of biomedical applications of rDNA technology using microbial organisms or laboratory animals. Nor does the report discuss in any detail the governance of biotechnology research funded by the federal government.

No single statute and no single federal agency govern the regulation of agricultural biotechnology products. As a general guide to a complex area of law, this paper provides only an overview of the regulatory paths that apply to products of agricultural biotechnology, as set out in applicable laws, regulations and guidelines. It does not discuss in detail the manner in which regulatory agencies address potential human or environmental risks, nor does it provide a substantive discussion of the technologies involved. Readers wanting more detailed information may want to refer to the sources noted at the end of this report. In addition, this report does not attempt to evaluate the adequacy, efficacy, or efficiency of the regulatory system, or evaluate the agencies' performances under these laws and regulations, issues which are the subject of continuing public debate. Nor does the report discuss current topics of debate such as labeling,

[1] DNA, or deoxyribonucleic acid, is the master molecule that encodes directions for all life processes.

public participation, and regulatory transparency. These and other issues are being addressed in other activities of the Initiative.

II. REGULATORY OVERVIEW

The products of rDNA technology include transgenic plants and animals, foods, and chemicals such as drugs, biologics, cosmetics, pesticides, and industrial feedstocks. Foods and chemicals produced by biotechnology are regulated under the federal statutes which govern the production and use of foods and chemicals generally. It is important to note that these statutes were written (1) before the development of rDNA technology and the proliferation of its products,[2] and (2) to address the properties of products and not their method of manufacture.

Current federal policy takes the position that agricultural products derived from rDNA technology can be appropriately regulated under current laws that regulate food and chemicals produced in a more traditional manner. The premise of this policy is that the safety evaluation of food and chemical products is based on the properties of the product, and not on the manner in which it was produced. Because of the assumption that rDNA technology is not inherently riskier than traditional production methods, federal policy has concluded that it is the properties of the rDNA technology product itself, rather than the production process, that should be the focus of regulation. For example, the 2000 National Research Council's report on genetically modified pest-protected plants reaffirmed its conclusions from a 1987 report:

- "There is no evidence that unique hazards exist either in the use of rDNA techniques or in the movement of genes between unrelated organisms."
- "The risks associated with the introduction of rDNA-engineered organisms are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods."
- "Assessment of the risks of introducing rDNA engineered organisms into the environment should be based on the nature of the organism and the environment into which it is introduced, not on the method by which it was produced."[3]

Regulation of agricultural biotechnology applies primarily at two distinct points in the development of a product: (1) the transgenic plant or animal itself (such as a transgenic crop), and (2) the products that are derived from the transgenic plant or animal (such as the food made from the transgenic crop).[4] In some cases, the transgenic plant or animal

---

[2] The Plant Protection Act, 7 U.S.C. 7701 *et seq.*, was passed in 2000; in large part it is a consolidation of authorities found in preexisting statutes, including the Federal Plant Pest Act and the Plant Quarantine Act. See note 5.

[3] National Research Council, *Genetically Modified Pest-Protected Plants: Science and Regulation,* (Washington, D.C. 2000) at p. 5, citing *Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues*, National Academy of Sciences.

[4] Biotechnology researchers who are recipients of grant money from the National Institutes of Health (NIH)

is the final product, as in the case of a lawn grass. More commonly, a plant or animal is modified to produce a desired product, such as a transgenic goat that is modified to produce a protein in its milk that has pharmaceutical value. The transgenic plant or animal might also be processed into a final product, such as corn that is modified to resist insect pests and also is processed into food products.

The federal statutes that are used to regulate the products of agricultural biotechnology give primary jurisdiction to three agencies: the Food and Drug Administration (FDA), the Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS), and the Environmental Protection Agency (EPA).

Under the Federal Food, Drug and Cosmetic Act (FFDCA), 21 U.S.C. 321 *et seq.*, FDA regulates food, drugs, cosmetics and medical devices. FDA uses its authorities under the FFDCA to ensure that food products derived through rDNA technology are safe to eat and that drug products derived through rDNA technology are safe and effective. (USDA's Food Safety and Inspection Service (FSIS) has inspection authorities for meat, poultry and eggs.) In addition, FDA is the agency primarily responsible for regulating the production of transgenic animals. The Plant Protection Act (PPA)[5] gives APHIS authority to regulate potential plant pests to ensure protection of commercial crops and the environment. APHIS uses this authority to impose regulatory restrictions on the importation, transportation and planting of transgenic plants.

Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), 7 U.S.C. 136 *et seq.*, EPA uses its authority to regulate transgenic plants that have been modified to produce a pesticidal substance, both to ensure that the production of such a pesticide in plants is safe for the environment, and to establish allowable levels of the pesticide in the food supply.

In addition to these statutes giving the agencies specific regulatory authorities, the National Environmental Policy Act (NEPA), 42 U.S.C. 4321 *et seq.*, imposes a procedural requirement that federal agencies evaluate the environmental impact of major federal actions significantly affecting the quality of the human environment. Although NEPA requires agencies to go through an environmental assessment process, it does not require agencies to make decisions based on that assessment. In addition, agencies have discretion to establish categorical exclusions from NEPA requirements. FDA, for example, has established categorical exclusions that include approvals of food additive

---

are required to follow research guidelines established by the Recombinant DNA Advisory Committee (RAC). Although these guidelines are voluntary for researchers who are not NIH grant recipients, they are widely considered to be the professionally accepted standard. The RAC serves in an advisory capacity to the Secretary of Health and Human Services, and was chartered in 1974 under the Public Health Service Act. 42 U.S.C. 282(b)(6). The functions of the RAC are governed by the provisions of The Federal Advisory Committee Act. 5 U.S.C. Appendix 2.

[5] Public Law No. 106-224. The Plant Protection Act repealed and consolidated the authorities of all or part of nine other statutes, including the Plant Quarantine Act of 1912 (7 U.S.C. 151-164a, 167), the Federal Plant Pest Act of 1957 (7 U.S.C. 150aa *et seq.* and 7 U.S.C. 147a note), and the Federal Noxious Weed Act of 1974 (7 U.S.C. 2801 *et seq.*), except the first section and section 15 of that Act (7 U.S.C. 2801 note and 7 U.S.C. 2814).

petitions. Further, many EPA actions are exempt from NEPA requirements because they are themselves environmental assessments.

If an action is deemed to fall within the scope of NEPA, typically an agency will perform an initial environmental assessment (EA) to determine whether the environmental issues that are implicated require a full environmental impact statement (EIS). Frequently, an agency will require an applicant in an approval process to submit an EA to facilitate the agency's environmental review. In an EIS, the agency must evaluate the environmental impacts of its decision and any alternative actions that might exist. It is beyond the scope of this paper to examine the application of NEPA to the specific agency determinations discussed in the report.

III. EVOLUTION OF THE REGULATION OF AGRICULTURAL BIOTECHNOLOGY

A. Asilomar and Its Antecedents

Early in the development of rDNA technology, scientists expressed concerns about the safety of the techniques employed to transfer genes from one organism to another. In particular, because much of the early work was performed using the genetic material available—mostly from bacteria and viruses—some scientists were concerned about the potential risks of generating new bacterial strains that might out-compete natural populations or transmit viral genes that might be involved in human cancer.

These concerns prompted two key meetings of scientists in the mid-1970s to discuss the potential risks associated with the use and subsequent manipulations of these genes. In January 1973, the National Science Foundation's Human Cell Biology Steering Committee and the National Cancer Institute (NCI) of the National Institutes of Health (NIH) convened a conference of scientists to deliberate on whether there was sufficient evidence to determine that viral genes used in early rDNA research were causally related to cancer in human beings. The consensus of that meeting was that the researchers should proceed cautiously, that they should attempt to quantify the potential risks of working with such genes, and that additional efforts should be expended to determine what safety precautions should be taken to avoid spreading a potential carcinogenic risk through the environment.

The 1973 meeting was followed by the now renowned 1975 Asilomar conference. This meeting reached beyond the specific issue of potential carcinogenic risks associated with the use of viral genes and gene fragments to address the overall safety issues associated with recombinant DNA techniques themselves. Although most of the participants believed that the technology neither posed significant health risks nor created new hazards, they agreed to abide by a set of research guidelines for the safe use of the technology. Chief among these was the agreement to limit work to disabled bacteria that were not able to grow outside a laboratory environment. Thus, one of the first recognized risk management decisions applied to the technology was the adoption of voluntary controls by an otherwise unregulated community of scientists, primarily in academic laboratories.

B. The Recombinant DNA Advisory Committee

In 1974 the Recombinant DNA Advisory Committee (RAC) was established to advise the Director of NIH on the safety of rDNA techniques.[6] In its charge to advise the Director of NIH, the RAC was instructed to evaluate rDNA technology for both its promise in uncovering basic aspects of health and disease, as well as consideration of "hypothetical hazards to public health and the environment and significant ethical, legal, and societal issues. The goal of the [RAC] is to consider the current state of knowledge and technology regarding DNA recombinants, their survival in nature, and their transferability to other organisms, and their societal impact."[7]

The RAC issued a set of Guidelines in 1976, consisting of a comprehensive set of rules governing the practices of rDNA technology and the facilities housing such research in order to prevent the inadvertent occupational exposure to or unintentional environmental release of either genetically modified organisms or the recombinant DNA itself. A wide margin of safety was imposed on the studies, including prohibition of certain types of experiments and the creation of special safety conditions, including various levels of containment.

Over time, as experience with transgenic organisms and the techniques for generating them increased, several of the less stringent constraints were lifted entirely, although a series of risk-based containment directives remain for the most hazardous research. Compliance with these guidelines is still compulsory for NIH-funded researchers, and voluntary (although largely adhered to) by institutions and investigators not funded by NIH. The application of the Guidelines within non-governmental institutions is ensured by Institutional Biosafety Committees (IBCs), which are registered with the NIH Office of Biotechnology Activities. Many experiments are thus reviewed and approved by the IBCs without any input from the RAC. Today, the RAC addresses human gene therapy applications almost exclusively and no longer focuses on issues relating to environmental releases.

C. The Coordinated Framework

In the 1980s, the application of existing statutes to biotechnology led to significant questions about overlapping authorities among the agencies, as well as uncertainties about whether the agencies would follow consistent approaches in using these authorities. In response to these concerns, the Reagan Administration created a Domestic Policy Council Working Group on Biotechnology, charged with drafting an overall federal framework for regulating biotechnology. In 1984, the White House Office of Science and Technology Policy (OSTP) proposed and in 1986 promulgated the Coordinated

---

[6] The authority of the RAC stems from 42 U.S.C. 282(b)(6), Section 402(b)(6) of the PHS Act, as amended. The Committee is governed by the provisions of The Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

[7] Http://www4.od.nih.gov/oba/rac/RACCharter.htm.

Framework for Regulation of Biotechnology (the Coordinated Framework) (51 Fed. Reg. 23,302 (June 26, 1986)). This document is considered a cornerstone of U.S. biotechnology policy, because it established principles for the federal regulation of biotechnology and clarified the roles and interactions of the various agencies.

The Coordinated Framework, however, is only a policy statement; it did not in itself establish new regulatory or legal requirements, although it did make several important points that have served as a foundation for subsequent policy and regulation. Key among these are the following principles:

- Existing statutes were deemed sufficient to provide agencies with the jurisdiction and authorities to ensure adequate regulation of biotechnology, although it was suggested that legislative actions could be taken as the field advanced.

- Safety assessments and other regulatory questions turned on the nature of the products, rather than on the manner in which they are produced–this concept is often referred to as "regulation of product, not process". The natural outcome of this principle is that products derived from biotechnology would be subject to the same kind of review given to the same kind of products produced in other ways.

- A lead agency was appointed in cases in which more than one agency had jurisdiction over the same category of products.

The policies embodied in the Coordinated Framework were similar to those expressed in the preceding Asilomar and RAC efforts. Perhaps the most important principle was that "the recently developed methods are an extension of traditional manipulations that can produce similar or identical products, they enable more precise genetic modifications, and therefore hold the promise for exciting innovation and new areas of commercial opportunity". 51 Fed. Reg. at 23,302.

Implicit in this statement is that the technology itself was not considered inherently risky; thus, appropriate regulatory oversight over the products of the technology would provide as stringent a control of risk (or determination of efficacy, where appropriate) as it would for traditionally-derived products.

Specific risk issues mentioned in the Coordinated Framework on which additional public comment was requested primarily addressed the issue of environmental risks associated with uncontained release from agricultural or other uses of biotechnology, including the potential for DNA to transfer from transgenic organisms to other organisms in the environment. The Coordinated Framework specifically discussed the need for appropriate risk assessment methodologies to be applied (and possibly developed) for organisms of higher potential risk on a "step-by-step" basis during the research and development process based on information incrementally derived from both traditionally- and transgenically-derived organisms.

At the same time, the Coordinated Framework explicitly indicated that the adequacy of those policies and laws should be reviewed periodically as the technology developed:

> "Although at the present time existing statutes seem adequate to deal with the emerging processes and products of modern biotechnology, there are always potential problems and deficiencies in the regulatory apparatus in a fast moving field. We believe this interagency coordinating committee should monitor the changing scene of biotechnology and serve as a means of identifying potential gaps in regulation in a timely fashion, making appropriate recommendations for either administrative or legislative action." 49 Fed. Reg. 50,858 (December 31, 1984).

IV. CURRENT REGULATION OF AGRICULTURAL BIOTECHNOLOGY

A number of factors determine which laws and regulations apply to a transgenic organism or a product derived from that organism, including

- the stage of development (*e.g.*, is it still in a contained laboratory setting, is it being field tested, or is it ready for commercial use in the United States);
- the intended uses (*e.g.*, is it intended for bioremediation of pollution or for biocontrol of another organism, is it intended to be a human drug or an animal biologic, or might it eventually be used as food even though that is not its primary use);
- the type of possible hazards (*e.g.*, does it have the potential to harm plants or contain new genetic material that might cause a plant to become a noxious weed, or does it have the potential to release pollutants into the atmosphere or bodies of water); and
- the type of organism (*e.g.*, is it an animal, plant, or microorganism).[8]

A. Regulation by Type of Organism

Figure 1 illustrates the regulatory pathway for products depending on the type of organism (*i.e.*, plant, animal, or microorganism) being modified. It also notes the application of NIH rDNA guidelines to the research and development phase of the transgenic organism.

[8] Council on Environmental Quality and the Office of Science and Technology Policy, *Case Studies of Environmental Regulation for Biotechnology*, January 2001 (http://www.ostp.gov/html/012201.html), hereinafter, CEQ-OSTP Case Studies.

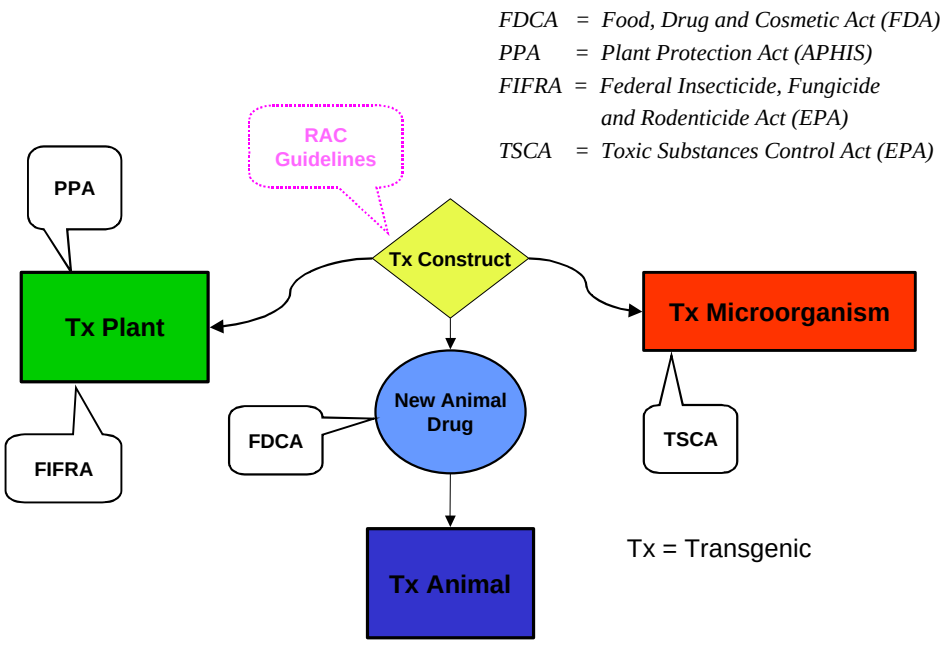

Figure 1

Transgenic plants are regulated by USDA's Animal and Plant Health Inspection Service (APHIS) under the Plant Protection Act (PPA) to control plant pests. Transgenic plants that have been modified to produce a pesticide are regulated by EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to ensure environmental and human health. Transgenic animals are regulated by FDA under the new animal drug provisions of the Federal Food, Drug and Cosmetic Act (FFDCA), although this is an area of regulation that is not yet well developed. EPA also may regulate substances produced by either a transgenic plant or an animal under the Toxic Substances Control Act (TSCA), which gives the agency authority to regulate new chemicals or new chemical uses that pose a risk of harm to human or environmental health. EPA does regulate certain transgenic microorganisms which it considers to be new chemical substances under TSCA.

1. Plants

The production of transgenic plants is regulated by two agencies. APHIS regulates transgenic plants to control potential plant pest risks. EPA regulates pesticidal substances produced by transgenic plants that have been modified to produce such substances (plant incorporated protectants, or PIPs). Figure 2 illustrates these regulatory pathways.

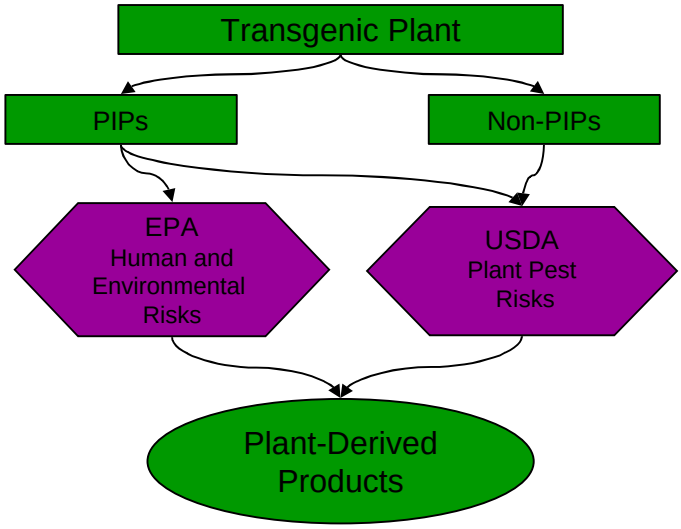

Figure 2

EPA also could assert jurisdiction, under TSCA, over transgenic plants that produce nonpesticidal chemicals. (59 Fed. Reg. at 45527, September 1, 1994.) At this time, however, EPA has not exercised this authority.

a) APHIS Regulation

Legal Authority. The importation, transportation, and planting of transgenic plants is regulated by APHIS under the Plant Protection Act (PPA). The PPA provides that the Secretary of Agriculture may

> "prohibit or restrict the importation, entry, exportation, or movement in interstate commerce of any plant, plant product, biological control organism, noxious weed, article, or means of conveyance, if the Secretary determines that the prohibition or restriction is necessary to prevent the introduction into the United States or the dissemination of a plant pest or noxious weed within the United States." Public Law No. 106-224, Section 411.

Under APHIS regulations, "regulated articles" are defined as "any organism which has been altered or produced through genetic engineering . . . which [USDA] determines is a plant pest or has reason to believe is a plant pest." 7 CFR 340.1. Section 403 of the PPA defines a plant pest as "a protozoan; a nonhuman animal; a parasitic plant; a bacterium; a fungus; a virus or viroid; an infectious agent or other pathogen," or similar articles that injure, damage, or cause disease in any plant or plant product.

Procedure under the Plant Protection Act. USDA uses its plant protection authority to require that anyone desiring to import, transport interstate, or release into the

environment (e.g., planting) a regulated article must apply for a permit or make a notification to APHIS that an introduction will be made. A permit imposes restrictions on transportation or planting to prevent the escape of plant material that may pose a pest risk to the environment. The notification procedure allows the introduction of plant material that may pose a plant pest risk without a permit, but only in accordance with specific criteria governing the type of material that is introduced and the steps that must be taken to ensure that it is environmentally contained. Obtaining a permit for field testing, or making a notification that testing will take place, is a typical step in the development of a commercial product.

Following field testing of a regulated article, a petition for nonregulated status may be submitted. For APHIS to grant a petition, the studies and data submitted in support of the petition, including the results of the field trials, must demonstrate that there will in fact be no significant plant pest risk from widespread planting. Petitioning APHIS for a determination of nonregulated status is a typical route to commercialization of a transgenic plant that will be widely planted, such as a commodity crop, since it allows planting and transportation without conditions that might be imposed by a permit. However, nonregulated status is not a precondition for commercialization. A product may also be commercialized under permit.

Permit. If a permit for environmental release is sought, the applicant must submit an application with information including

- the donor organism(s);
- the recipient organism(s);
- the vector or vector agent(s);
- a description of the molecular biological mechanisms involved in the production of the regulated article;
- a description of the activity of the modified genetic material in the regulated article and a comparison to an unmodified organism;
- a description of the purpose of the introduction; and
- steps to control the article and associated biological materials. 7 CFR 340.4.

According to APHIS procedures, it reviews the submitted data to evaluate a number of potential risks, including whether the transgenic plant might: (1) expose other plants to pathogens; (2) harm other organisms, including agriculturally beneficial organisms, threatened and endangered species, and, in the case of plants that produce pesticides, organisms that are not the intended target of the pesticide (non-target organisms); (3) increase weediness in another species with which it might cross; (4) have an adverse effect on the handling, processing or storage of commodities; or (5) threaten biodiversity.

Applicants seeking APHIS approval for importation or interstate movement may obtain limited permits for those purposes. Applicants may also request non-renewable, comprehensive permits good for 13 months, under which multiple phenotypes, genes, and donors and all anticipated test release sites and movements for a

single crop are included in a single package. All genes to be tested in that crop (including uncharacterized genomic project genes not eligible under notification) can be included. Field test reports must be submitted within six months after termination of the field test. 7 CFR 340.3(d)(4).

Notification. The notification process is an expedited route to introduction of a transgenic plant. It can take the place of the permit process for importation, transportation or environmental release. It is available for plant species that are not listed by APHIS as a noxious weed (listed at 7 CFR Part 360) and are not considered a weed in the area of the proposed release, provided that specific criteria and certain performance standards are met. The performance standards govern how plants that are approved pursuant to the notification procedure should be shipped, stored, planted and field tested to ensure that regulated articles do not escape from containment or persist in the environment. 7 CFR 340.3(c). Acknowledgements for environmental release notifications apply to field testing for one year from the date of introduction, and may be renewed annually by submitting an additional notification. 7 CFR 340.3(e)(4).

The notification eligibility criteria cover characteristics of the regulated articles that are relevant to their risk profile as a plant pest, and require that:

- The plant species be a species APHIS has determined may be safely introduced;
- The introduced genetic material is stably integrated;
- The function of the introduced genetic material is known and its expression in the regulated article does not result in plant disease;
- The introduced genetic material does not produce an infectious entity, toxicants to nontarget organisms likely to feed or live on that plant species, or products intended for pharmaceutical use;
- The introduced genetic sequences derived from plant viruses do not pose a significant risk of the creation of any new plant virus; and,
- The plant has not been modified to contain certain genetic material derived from an animal or human pathogen. 7 CFR 340.3(b).

To make a notification, the applicant sends a letter to APHIS, including such information as designation of the transformed line, the category of modification, the phenotype and genotype of each transformant line, and a brief summary of the elements in the constructs. Within five days of receipt of the notification, APHIS will provide a copy to the regulatory officials in the appropriate states. APHIS will respond to the notification with an acknowledgement or denial within ten days for an interstate shipment notification or within thirty days for an importation or environmental release notification. An application whose notification is denied may apply for a permit.

Petition for Nonregulated Status. Following planting experience and data collection under either a permit or a notification, a person may petition APHIS for a "determination of nonregulated status," which is a determination that a particular article previously regulated as a potential plant pest will no longer be regulated, on the basis of accumulated

evidence that the article does not in fact pose a plant pest risk. 7 CFR 340.6. Nonregulated status permits the unrestricted transportation and planting of the crop, and is often sought for full commercialization, especially for commodity crops. A person may request that APHIS extend a previous determination of nonregulated status to other organisms, based upon information showing the similarity of the nonregulated organism and the regulated articles in question.

b) EPA Regulation

Legal Authority. Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), EPA has the authority to regulate the manufacture, sale and use of pesticides in order to protect the environment. 7 U.S.C. 136 *et seq.* Therefore, a substance produced and used in a living plant, whether through conventional breeding or through genetic modification, is regulated by EPA if it is intended to control pests. These substances, often referred to as plant pesticides, are now referred to by EPA as plant-incorporated protectants (PIPs). 66 Fed. Reg. 37,772 (July 19, 2001); 40 CFR Parts 152 and 174.

It is important to note that EPA's authority under FIFRA stems from the plant's pesticidal properties and not from the plant itself; plants used as food are subject to FDA food safety authorities, and plant pests are regulated by USDA-APHIS. For example, Bt corn contains genes from the bacterium *Bacillus thuringiensis* (Bt) that express an insecticidal protein. EPA determined that the inserted genes and the expressed toxin were subject to its authority to regulate pesticides under FIFRA.

FIFRA requires that a pesticide not cause "unreasonable adverse effects on the environment," 7 U.S.C. 136a(c)(5), which is defined to mean "(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 inconsistent with the [standard under the] Federal Food, Drug, and Cosmetic Act." 7 U.S.C. 136(bb).[9]

Therefore, EPA regulates PIPs both to determine their environmental safety when produced by the living plant and to establish levels at which their presence in food is safe for consumption (*i.e.*, sets tolerances).

Notifications and Experimental Use Permits. Prior to full-scale commercial use, EPA regulates pesticides through notifications and Experimental Use Permits (EUPs). For genetically-modified pesticides, EPA requires only a notification for small scale field tests, defined as less than 10 acres of land or 1 acre of water, and where some confinement measures are taken. Larger field tests, up to 5000 acres, require an EUP to gather reliable data to support a registration process. Field tests larger than 5000 acres generally require a full registration. 7 U.S.C. 136(c); 40 CFR Parts 152 and 172.

[9] This second criterion was added by the Food Quality Protection Act (FQPA) in 1996. Public Law 104-170.

Registration Process under FIFRA. FIFRA provides, with some exceptions, that no person may distribute or sell in the United States any pesticide that is not registered. 7 U.S.C. 136a(a). Pesticides are defined by FIFRA as "(1) Any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, (2) any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant, and (3) any nitrogen stabilizer." 7 U.S.C. 136(u).

Pursuant to its regulations under FIFRA, EPA requires that pesticide manufacturers obtain a registration. Through the registration process, EPA determines whether the intended use of the pesticide is safe for the environment, and places conditions upon its use to ensure that environmental safety is protected. Once a pesticide has been registered, it may be sold and distributed in the United States.

Before EPA will grant the registration of a pesticide, the applicant must show that the pesticide "when used in accordance with widespread and commonly recognized practice, . . . will not generally cause unreasonable adverse effects on the environment". 7 U.S.C. 136a(c)(5). FIFRA defines the environment as "water, air, land, and all plants and man and other animals living therein, and the interrelationships which exist among these." 7 U.S.C. 136(j). EPA's evaluation includes an assessment of data from tests done by the producer of the pesticide according to EPA guidelines, and an evaluation of whether a pesticide has the potential to cause adverse effects on humans, wildlife, fish and plants, including endangered species and non-target organisms, as well as possible contamination of surface water or groundwater.

Exemption from Registration

FIFRA allows EPA to exempt from registration requirements a pesticide or category of pesticides for which registration is not necessary to meet the goal of environmental protection. 7 U.S.C. 136w(b)(2). To qualify for an exemption under EPA regulations, a pesticide must pose a low probability of risk to the environment (including humans and other animals, plants, water, air and land) and be unlikely to cause unreasonable adverse effects to the environment even in the absence of regulatory oversight. 40 CFR 152.25.

If a pesticide or its chemical residue may appear in food, then it can only meet these exemption criteria if it also meets the food safety standard under FFDCA that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." 21 U.S.C. 346a(c)(2)(A). FFDCA gives EPA the authority to set allowable levels ("tolerances") of pesticide chemical residue in food, and, under this standard, to exempt qualified pesticides from the tolerance requirement.

Pesticide Food Tolerances. Under the FFDCA, food is deemed adulterated, and therefore prohibited from sale, if it, among other things, "bears or contains any poisonous or

deleterious substance which may render it injurious to health." 21 U.S.C. 342. The FFDCA states that a pesticide chemical residue in or on food is not safe unless it meets a tolerance (maximum allowable) level that EPA has established for that pesticide or EPA has exempted the pesticide from the requirement of a tolerance for the residue. 21 U.S.C. 346a(a)(1).

The FFDCA authorizes EPA to exempt a pesticide from the requirement of a tolerance if "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." 21 U.S.C. 346a(c)(2)(A). In determining whether a pesticide chemical residue is safe, EPA must consider "available information regarding the aggregate exposure levels of consumers . . . to the pesticide chemical residue and to other related substances, including dietary exposure under the tolerance and all other tolerances in effect for the pesticide chemical residue, and exposures from other non-occupational sources." 21 U.S.C. 346a(b)(2)(D)(vi). As noted above, this is the standard that EPA uses to evaluate human dietary risk when determining whether to exempt a pesticide used in food from FIFRA registration requirements.

However, FIFRA does not provide for exemption of a pesticide in food based solely upon consistency with the FFDCA section 408 exemption standard. At a minimum, EPA also must evaluate risks arising from occupational exposure to humans and determine that such risks meet both exemption criteria. In addition, EPA must evaluate the risks to the environment from the pesticide and determine both that the pesticide poses only a low probability of environmental risks, and that use of the pesticide is not likely to cause any unreasonable adverse effects on the remainder of the environment in the absence of regulation under FIFRA.

Regulation of PIPs. EPA defines a plant incorporated protectant (PIP) as "a pesticidal substance that is intended to be produced and used in a living plant, or in the produce thereof, and the genetic material necessary for the production of such a pesticidal substance. It also contains any inert ingredient contained in the plant, or produce thereof."[10] 40 CFR 174.3. If EPA did not include the relevant genetic material in the definition of a PIP, then the genetic material would be considered simply part of the whole plant and consequently exempt from FIFRA. EPA regulates the pesticidal protein expressed by the plant, not the plant itself.

Under recently finalized rules, EPA exempts PIPs derived through conventional breeding from sexually compatible plants from registration requirements under FIFRA, as long as the genetic material has never been derived from a source that is not sexually compatible with the recipient plant. 66 Fed. Reg. 37,772 (July 19, 2001); 40 CFR 174.25.

[10] A pesticide as defined by FIFRA need not be a substance that kills a pest, but may instead be a substance that prevents, repels or mitigates a pest. " 'Genetic material necessary for the production' " means both: Genetic material that encodes a substance or leads to the production of a substance, and regulatory regions. It does not include noncoding, nonexpressed nucleotide sequences." 40 CFR 174.3.

These exempt PIPs are still subject, however, to EPA's adverse event reporting requirements. 40 CFR 174.1.

In its recent rules, EPA also exempted from the requirement of a tolerance the residues of nucleic acids that are part of a PIP. 66 Fed Reg 37,817 (July 19, 2001) 40 CFR Part 174.475. In establishing this exemption, EPA noted that nucleic acids are found in all life forms, have always been present in food, and are not known to cause any adverse health effects when consumed in food.

2. Animals

a.) FDA

FDA is likely to have regulatory authority over transgenic animals under FFDCA, although the agency has not yet clearly articulated the reach of that authority. The FFDCA may be read to provide FDA regulatory authority over (1) the genetic construct inserted into the animal's genome; (2) any product of that construct whose intended use is to affect the animal itself; and (3) any product of that construct whose intended use is as a food, drug, or biologic.

First, the construct inserted into the genome of the animal (the "genetic construct") is itself an animal drug, because it meets one of the statute's definitions of a drug as "articles (other than food) intended to affect the structure or any function of the body" of the animal. 21 U.S.C. 321(g)(1). Therefore, the genetic modification of an animal outside of initial laboratory research is likely to require FDA's approval under its animal drug regulations.[11] At least one application is pending before FDA for approval of a transgenic animal under animal drug regulations—a salmon modified to produce a growth hormone that causes the salmon to reach market size more quickly. Because the process has not yet been completed for any animal, however, it is not clear how FDA will implement this authority, and it may be continuing to develop its policy approach in this area.

Second, if the inserted genetic materials produce a drug or biologic in the body of the animal that affects the animal itself (such as a growth hormone), then both the genetic construct and the produced drug each could require approval as a new animal drug. Because both of those animal drugs could be present in subsequent generations, FDA's approvals, and any conditions on those approvals, could apply to those subsequent generations.

Finally, if the genetically modified animal produces a food, drug, or biologic—for example, by expressing a therapeutic protein in its milk—FDA's regulatory reach also

[11] See case studies on "Growth-Enhanced Salmon" and "Farm Animal (Goat) That Produces Human Drugs" included in the CEQ-OSTP Case Studies, *supra* note 8, in which it is stated that this is the regulatory approach that FDA will take. Note that FDA does not require prior approval to conduct initial laboratory research on a new animal drug, or a new human drug or biologic.

would appear to extend to that product. As noted below, such a genetically modified animal could be considered a production facility or bioreactor for regulatory purposes. Figure 3 illustrates FDA regulatory coverage of transgenic animals.

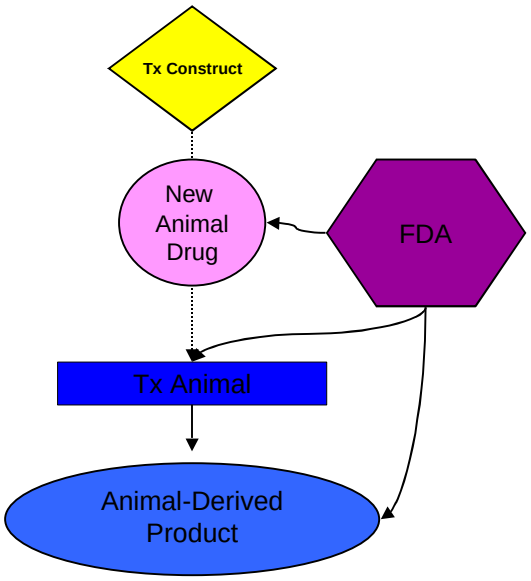

Figure 3

New animal drug approval process. The FFDCA provides that no new drug may be introduced into interstate commerce unless the FDA has approved an application for such use. 21 U.S.C. 355. A "new animal drug" is an animal drug that is "not generally recognized . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. 321(v). The FFDCA prohibits the manufacture of any drug that is adulterated, and a drug that is a new animal drug is deemed to be adulterated if is unsafe. 21 U.S.C. 331(g) and 351(a)(5). Further, a new animal drug is deemed unsafe if its use or intended use is not approved pursuant to an application filed with FDA. 21 U.S.C. 360b(a)(1).

Therefore, it is likely that new animal drugs may never be produced outside of a purely research setting without FDA's approval of an Investigational New Animal Drug application (INAD) for clinical trials (to demonstrate safety and efficacy) and subsequently of a New Animal Drug application (NADA) for commercialization of the drug (based on data generated by the clinical trials). 21 CFR Parts 511 and 514. An NADA must contain information supporting (1) safety of the target animal and human food; (2) efficacy of the drug; (3) methods for detecting drug residue in food-producing animals; (4) current good manufacturing practices; and (5) an environmental assessment of the effects of using the drug in food-producing animals.

Under the FFDCA, drugs are deemed adulterated if their manufacturing processes do not meet standards sufficient to assure the safety, identify, strength, quality and purity that are claimed for the drug. 21 U.S.C. 351(a)(1). To address manufacturing issues,

FDA has in place regulations establishing and overseeing good manufacturing practices (GMPs) for drug production facilities. Therefore, FDA could apply GMP regulations to the creation of transgenic animal that is modified to produce a drug (*e.g.,* in its milk), by deeming that animal to be a production facility.

Because the approval criteria for a new animal drug include its intended use, FDA's new animal drug approval process would likely take into consideration the end use of the animal and/or products derived from the animal as a result of the genetic modification. Therefore, FDA's regulatory reach may extend to control of food and drug production via transgenic animals even before the final products are submitted to FDA for approval.

b.) EPA

EPA has stated that it has the authority under TSCA to regulate genetically modified animals when they are used for a purpose not excluded by section 3 of that Act.[12] However, to date, EPA has not applied TSCA to genetically modified animals.

3. Microorganisms

TSCA provides EPA with authority to regulate chemical substances which may present an unreasonable risk of injury to health or the environment during manufacture, processing, distribution in commerce, use, or disposal. TSCA applies to uses of substances that are not specifically covered by another statute (*e.g.*, pesticides regulated under FIFRA, or drugs regulated under FFDCA).

A "chemical substance" is defined to include "any organic or inorganic substance of a particular molecular identity, including any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature and any element or uncombined radical." 15 U.S.C. 2602(2)(A). EPA has interpreted the definition of a chemical substance to cover intergeneric microorganisms (microorganisms created by the insertion of genes from another genera).[13] 40 CFR Part 725. If a microorganism is not intergeneric (*e.g.*, intrageneric or naturally occurring), EPA has general authorities to address safety concerns that might arise. 15 U.S.C. 2603-2607.

Examples of commercial uses of microorganisms subject to TSCA include specialty chemical and enzyme production, bioremediation, biosensors of environmental contaminants, biofertilizers, ore mining, oil recovery, and biomass conversion.

[12] This position is taken in several case studies published in the CEQ-OSTP Case Studies, *supra* note 8.

[13] EPA has defined intergeneric microorganisms as those microorganisms resulting from the deliberate combination of genetic material originally isolated from organisms classified in different genera: for example, a *Pseudomonas* sp. bacterium, with DNA from an *Escherichia* sp. bacterium, would be considered intergeneric. 40 CFR 725.3.

EPA uses its authorities under TSCA to require that manufacturers of a covered substance submit a premanufacture notification (PMN). 15 U.S.C. 2604. EPA's TSCA biotechnology regulations have established a notification specifically designed for microorganisms: the Microbial Commercial Activity Notice (MCAN). 62 Fed. Reg. 17,190, April 11, 1997; 40 CFR 725.3 and 725, Subpart D. An MCAN must be submitted to EPA at least 90 days before intergeneric microorganisms are used for commercial purposes, and EPA has 90 days to review the submission. During the review period, EPA may take action to prohibit or limit the production, processing, sale, use, and disposal of microorganisms that raise health or environmental concerns.

EPA reviews the microorganisms for their potential to cause unreasonable risks to human health and the environment. 15 U.S.C. 2604(a). TSCA does not define "unreasonable risk," but it lists criteria to be considered that include both the extent to which risks would be avoided by regulation and the burden imposed by that regulation. 15 U.S.C. 2605(c)(i); see also 2604(b)(4)(A)(ii). If EPA identifies any unreasonable risks, it must act to prevent those risks before the microorganism can be manufactured or imported either for research and development, or on a commercial scale. 15 U.S.C. 2604(f); see also 40 CFR Part 725.

The TSCA biotechnology regulations also address intergeneric microorganisms used in research and development for commercial purposes and create a vehicle for reporting on testing of new microorganisms in the environment—the TSCA Experimental Release Application (TERA). 40 CFR 725.3 and 725, Subpart E. A TERA must be submitted to EPA at least 60 days prior to initiating such field trials. The TERA is intended to be more flexible than the MCAN, in order to meet the needs of researchers, and the review period is shortened to 60 days for a TERA application.

An MCAN need not be submitted for intergeneric microorganisms when criteria are met that define eligible microorganisms, introduced DNA, and containment practices. This exemption is most applicable to specialty and commodity chemicals, including industrial enzymes. Intergeneric microorganisms used for research in contained structures are exempt from EPA reporting requirements, but researchers must maintain records demonstrating eligibility for exemption. In addition, certain intergeneric microorganisms also are exempt from reporting requirements when used in field tests because prior test experience indicates low environmental risk.

B. Regulation of Products Derived From Transgenic Organisms

The regulation of biotechnology starts with categories of products whose properties and intended uses determine their regulatory pathways. For example, a product might be regulated as either a drug or a dietary supplement, depending on the claims for the product made by the producer. If it purports to cure a disease, it would be regulated as a drug and come under the FFDCA requirements. If the claim is simply that it promotes some aspect of health, it would fall under the less stringent requirements of dietary supplements under the Dietary Supplement Health and Education Act (DSHEA).

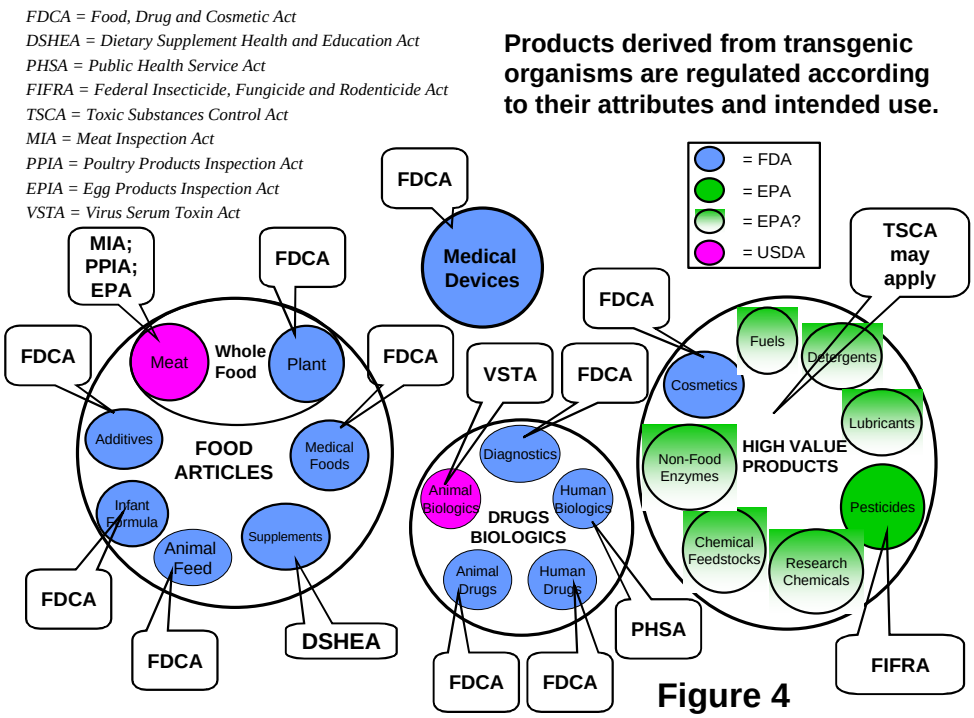

Figure 4

Figure 4 illustrates a broad array of products, virtually all of which theoretically can be produced from transgenic plants, animals, or microorganisms. In this illustration, the statutes that govern different categories of products are identified, as well as the agencies responsible for regulating the category under each statute. The green and white categories are those that conceivably could be regulated by EPA under TSCA if they both were not regulated under another statute and posed an unreasonable risk of harm to people or the environment.

1. Food

The FDA is the lead regulatory agency of food articles, with safety and labeling authority for most whole foods, food additives, and dietary supplements; similar authorities apply to animal feeds. USDA's Food Safety and Inspection Service (FSIS) has safety inspection and approval authority for meat, poultry, and egg products. Medical foods and infant formulas are categories of food to which some additional regulations apply, and will not be discussed in this paper. Alcoholic foods (beer, wine, and liquor) are regulated separately by the Bureau of Alcohol, Tobacco and Firearms of the Department of the Treasury and also are not addressed here.

a.) Whole Foods and Food Additives

Under the FFDCA, food is deemed adulterated if it, among other things, "bears or contains any poisonous or deleterious substance which may render it injurious to health … or if it bears or contains any food additive that is unsafe … or a new animal drug (or

conversion product thereof) that is unsafe." 21 U.S.C. 342. Food may be marketed unless it can be shown to be "ordinarily injurious to health." 21 U.S.C. 342(a)(1). Whole foods fall under this general adulteration provision, and the responsibility is on the marketer of a food to ensure its safety; no FDA approval prior to marketing is required. FDA has authority under the FFDCA, however, to seize adulterated food, enjoin its distribution or sale, and refer offenders for criminal prosecution.

Substances that are added to food, on the other hand, fall into two possible categories: food additives and substances that are "generally recognized as safe." Food additives require premarket review and approval by FDA as "safe", which is defined as "a reasonable certainty of no harm … from the intended use of the additive." 21 CFR 170.3(i). If a food additive is deemed unsafe, the food containing the additive is deemed adulterated and cannot be marketed. 21 U.S.C. 331(a), 342(a)(1), 342(a)(2)(C). If the substance added to food, however, is "generally recognized as safe" (GRAS), then it is not considered a food additive for purposes of the FFDCA and no prior FDA approval is required.[14] 21 U.S.C. 321(s); 21 CFR § 170.30.

FFDCA does not require FDA to make a premarketing determination that a potential food additive is GRAS; that determination is made by the food manufacturer without FDA review. The FDA does, however, have a voluntary "affirmation" process under which a manufacturer may ask for pre-market guidance on whether a substance is GRAS. 21 CFR 170.35(c)(4) and (c)(5). In 1997, FDA proposed new regulations further defining the appropriate basis for a GRAS claim, and proposing a new voluntary pre-market review process by which manufacturers could notify the FDA of a GRAS exemption claim. 62 Fed. Reg.18,938 (April 17, 1997). Although these proposals have not yet been finalized, FDA invited the submission of GRAS notifications pursuant to the proposal, and has received several dozen such notices.

1992 Policy Statement. In 1992, FDA published a policy statement regarding food derived from genetically modified plants. 57 Fed. Reg.22,984 (May 29, 1992). In that statement, FDA proposed to consider foods derived from genetically modified plants in the same way that it had traditionally treated foods containing additives developed through more traditional forms of plant breeding. Both the construct and the proteins resulting from the gene(s) could be considered food additives.

FDA also indicated that most foods derived from genetically modified plants were presumptively GRAS. For example, constructs used to make the transgenic organisms from which food articles are derived are likely GRAS, as DNA is present in all living organisms and has been consumed without adverse effect. FDA made clear, however, that the gene products, which may include proteins, carbohydrates, fats and oils, should be scrutinized more carefully for safety. If such substances were the same or similar to

[14] Congress defined food additive as "any substance the intended use of which results or may reasonable be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food … *if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures . . . to be safe under the conditions of its intended use."* 21 U.S.C. 321(s) (emphasis added)

those already found at similar or greater levels in food, then they most likely would be considered GRAS. If those substances differed significantly in structure, function or composition from substances currently found in food, then premarket approval as a food additive would be required under FFDCA Section 409.[15]

In its 1992 Policy Statement, FDA created a voluntary process under which producers could consult with the agency about safety and regulatory issues prior to marketing food derived from rDNA technology. Typically, the developer of the product initiates a consultation with FDA, submits summary information about the safety and nutritional assessment of the product, and makes a scientific presentation to FDA scientists.

Relevant safety issues addressed during the consultation process include the source(s) of introduced genetic material, information pertaining to the agronomic and quality attributes of the plant, genetic analysis of the modification and stability of expected genomic traits (*e.g.,* Southern blot analysis of the introduced gene(s) and restriction fragment length polymorphisms), evaluation of the safety (toxicity and allergenicity) of newly introduced proteins, and chemical analyses of important toxicants and nutrients. Underlying this review process is the determination of whether the genetically modified food is substantially equivalent to, and as safe as, the parental species from which it was derived. 57 Fed. Reg. at 22,992.

FDA's position is that this informal consultation process allows it to identify unresolved safety issues without going through the food additive regulatory process. It is important to note, however, that under the voluntary consultation process the manufacturer, not FDA, makes the determination of safety; therefore, the burden of proof regarding safety remains with the manufacturer.

2001 Proposed Regulations. In January 2001, FDA published proposed regulations on two relevant subjects: a mandatory pre-market notification process for genetically modified foods, 66 Fed. Reg. 4706, (January 18, 2001), and voluntary guidance for labeling genetically modified foods, 66 Fed. Reg. 4839, (January 18, 2001).[16]

The proposed regulations would require the pre-market submission to FDA of a Premarket Biotechnology Notice ("PBN") containing the following information relevant to the food derived from a genetically modified source (66 Fed. Reg. at 4732-4733):

- A description of the purpose of the modification;
- A description of identities of the host plant and donor DNA and information on how the genetically modified plant was engineered;

[15] To date, the only genetically modified food that has triggered the food additive process is the FLAVR SAVR™ tomato. FDA approved the selectable marker gene encoding resistance to the antibiotic kanamycin (*kan*^{r}) and its gene product (amino glycoside 3'-phosphotransferase II (APTII)) as a food additive. 59 Fed. Reg. 26,700 May 23, 1994.

[16] The issue of labeling is beyond the scope of this paper and the FDA proposal is not discussed here.

- Information on the nature and levels of substances (including toxic substances and antinutrients) introduced into the food;
- An estimate of dietary exposures to the food;
- "Data or other information" comparing the composition and characteristics of the genetically modified food to those of comparable food;
- A discussion of "available data" on the allergenic and toxic potential of the modified food;
- A description of any applications or uses that are not suitable for the genetically modified food;
- A description of the regulatory status of the food in other agencies in the United States and elsewhere in the world.
- A certification from a responsible official in the company that the genetically modified food is as safe as comparable food and an explanation of why that conclusion is justified.

Within 120 days of receiving the PBN, FDA would send the manufacturer an evaluation of the manufacturer's conclusion that the food derived from the genetically modified plant was GRAS. As with the prior voluntary premanufacturing consultation process, the FDA itself makes no determination regarding the safety of the food. The content of the PBN, as well as the response to the PBN, as a general matter, would be available to the public. Parties submitting PBNs would be prohibited from marketing these foods until FDA has responded favorably to the PBN.

b.) Meat

FDA. As noted in the first section, the FDA could take the position that the construct used to create a transgenic animal constitutes a "new animal drug" for the purposes of the FFDCA, requiring premarket approval. As noted above, the FFDCA provides that food is considered adulterated if it contains an unapproved animal drug or a conversion product of that drug. Therefore, FDA might require approval of the consumption of a transgenic animal, although it has not issued clear guidance in this area.

USDA. In addition to possible FDA approval, slaughter of transgenic animals for consumption may require approval by the Food Safety and Inspection Service (FSIS) of USDA. Under the Meat Inspection Act, USDA has authority to prohibit in commerce meat and meat food products that are adulterated. 21 U.S.C. 601 *et seq.*; 9 CFR Part 301. The term adulterated is defined in both statute and regulation to mean, among other things, that the meat "bears or contains any poisonous or deleterious substance which may render it injurious to health."

Under 9 CFR 309.16, "livestock suspected of having been treated with or exposed to any substance that may impart a biological residue which would make the edible tissues unfit for human food or otherwise adulterated" shall be condemned. Therefore, the Meat Inspection Act appears to give FSIS the discretion to declare a construct an adulterant if there is some element of risk from the construct or its expression product(s).

A difficult ancillary issue will be the development of validated systems that not only can identify transgenic animals before they enter the slaughterhouse, but also distinguish between transgenic animals that are approved for human consumption and those that are not.

c.) Dietary Supplements

Dietary supplements, regulated under the Dietary Supplement Health and Education Act (DSHEA) (P.L. 103-417), are not subject to the premarket safety evaluations required of food additives. 21 U.S.C. 321(s)(6). Although it is the obligation of manufacturers to develop adequate evidence to determine that the dietary supplements they manufacture or distribute are safe, they are not required to provide FDA with the evidence relied upon to substantiate safety or effectiveness before or after the products are marketed.

Therefore, FDA has the burden of proof in determining that a dietary ingredient is unsafe. Also, unlike drug products, manufacturers and distributors of dietary supplements currently are not required by law to record, investigate, or forward to FDA any reports they receive of injuries or illnesses that may be related to the use of their products.

For example, marketing a dietary supplement produced from the milk of a transgenic cow would not require any premarket approval under DSHEA, which provides that the manufacturer of a dietary supplement need only demonstrate that the supplement is safe. Therefore, FDA's regulatory reach under DSHEA is limited to a self-initiated postmarket determination of risk, regardless of whether the dietary supplement was derived using rDNA technology or more traditional methods.

2. Drugs and Biologics

The FDA is responsible under the FFDCA for regulating and approving products whose intended use is as human and animal drugs; under the Public Health Service Act (PHSA), 42 U.S.C. 201 *et seq.*, FDA regulates products whose intended use is as human biologics. The regulatory responsibility for animal biologics rests with USDA.

a.) Human and Animal Drugs and Human Biologics (FDA)

Under the FFDCA, the FDA must approve human and animal drugs for safety and efficacy before they can be marketed in the United States. 21 U.S.C. 355. A drug is defined as a substance "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals and articles (other than food) intended to affect the structure or any function of the body of man or other animals." 21 U.S.C. 321(g)(1). Similar authority is given to the FDA for human biologics under the PHSA, to ensure that biologics are safe, pure and potent. A human biologic is defined as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative,

allergenic product, or analogous product … applicable to the prevention, treatment, or cure of a disease of condition of human beings." 42 U.S.C. 262(i).

In addition to approving the drug or human biologic, the FDA also has responsibility for ensuring that the drug or biologic manufacturing process ensures the safety, purity, and effectiveness of the therapeutic product. FDA holds manufacturers responsible for meeting current good manufacturing practices (GMPs).[17] This authority suggests that FDA may have regulatory reach over the creation and management of the genetically modified animals or plants producing the drug or biologic, in a manner analogous to its oversight of more traditional drug manufacturing facilities. At the present time, however, FDA has not issued GMPs that apply specifically to the production of drugs or biologics from genetically modified animals or plants. [18]

Animals. As noted above, the construct inserted into the genome of the animal constitutes a "new animal drug" that must be approved by FDA under the FFDCA. In addition, the animal may be genetically modified to create a protein (in its milk, for example) that itself could constitute a human or animal drug or a human biologic. As noted earlier, the approval criteria for a new animal drug include its intended use. Therefore, FDA's regulatory reach may extend to control of drug and biologic production via transgenic animals even before the products themselves are submitted for approval.

Plants. If a plant is modified to create a protein intended to be used as a human or animal drug, or human biologic, the product derived from the plant would be regulated in the normal course under FDA drug and biologic approval regulations. Unlike the transgenic animal case, however, the construct used to create a transgenic plant would not require FDA approval because it is not an "animal" drug. Therefore, FDA's regulatory review of transgenic plants that create drugs or biologics would likely be limited to the imposition of GMPs.

As previously discussed, USDA (APHIS) permits genetically modified plants used to create drugs or biologics if it appears that such plants would constitute a a plant pest risk under the Plant Protection Act.

b.) Animal Biologics (USDA)

The Virus Serum Toxin Act (VSTA) requires that any "virus, serum, toxin, or analogous product intended for use in the treatment of domestic animals" be prepared only under license from the U.S. Department of Agriculture (USDA). 21 U.S.C. 151 *et seq.* Therefore, if a transgenic animal is producing an animal biologic, the Animal and

[17] Under the FFDCA, drugs are deemed adulterated, and therefore unlawful to sell, if "the methods used in, or the facilities or controls for, its manufacture, processing, packing, or holding do not conform to or are not operated in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." 21 U.S.C. § 351(a)(1).

[18] In 1995, FDA published a document entitled *Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals.*

Plant Health Inspection Service of USDA (APHIS) is the regulatory agency with jurisdiction over the approval of that biologic. (As noted above, FDA's Center for Veterinary Medicine has jurisdiction over animal drugs such as antibiotics.)

USDA has defined biological products, for the purposes of regulating under VSTA, as "all viruses, serums, toxins (excluding substances that are selectively toxic to microorganisms, *e.g.*, antibiotics), or analogous products at any stage of production, shipment, distribution, or sale, which are intended for use in the treatment of animals and which act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response." 9 CFR 101.2.

3. High-Value Products

As noted previously, animals and plants can be genetically modified to produce chemicals that could have a wide variety of non-food uses. In addition to the human and animal biomedical applications discussed above, chemicals produced by plants and animals could include fuels, industrial chemicals and enzymes, cosmetics, pesticides, detergents, lubricants, and chemical feedstocks. As with other products derived from genetically modified plants, animals, and microorganisms, the regulation of such items will depend on the nature of the product produced. Some of the more likely possibilities are discussed below.

a.) Pesticides

As noted previously, EPA has jurisdiction over pesticide products under FIFRA. Plants or microorganisms that express their own pesticides are regulated as discussed in prior sections. But it is also possible to genetically engineer a plant to produce a protein that is extracted from the plant or animal and made into a pesticide. In such a case, the plant effectively functions as a chemical production facility.

The chemical that would be extracted and marketed as a pesticide would be required to be registered in accordance with the FIFRA process discussed earlier. The question is whether the plant itself would come under any additional regulatory review. If the pesticide works to protect the plants while the plants are being grown, then they would be "plant incorporated protectants" subject to EPA and USDA (APHIS) review.

On the other hand, if the chemical produced has pesticidal properties but is not intended to be used as a pesticide, then EPA would not have authority to regulate that substance as a pesticide under FIFRA. If that substance were toxic and posed a human or environmental risk, then EPA might have authority to regulate it under TSCA. In any case, the genetically modified plant would be subject to the USDA (APHIS) review under the Plant Pest Protection Act. The FDA would remain responsible for overseeing the safety of any food or feed derived from the plant.

b.) Industrial Chemicals

Industrial chemicals produced by genetically modified plants or animals, and not otherwise covered by a specific statute, would be regulated in the same manner as other industrial chemicals. For example, a new chemical might be subject to TSCA's premanufacturing notification requirements. However, if the chemical is one previously manufactured and does not fall within TSCA or one of the specific regulated categories noted above, there likely would be no federal regulatory review of the chemical being produced. In effect, the regulatory system would treat the production of a chemical through a genetically engineered plant or animal simply as a novel manufacturing process to create an already existing chemical. If the plant or animal were also intended for use in food of feed or some other regulated purpose, then it would be reviewed under the statutes noted previously.

As noted previously, the genetically modified plant or animal would itself be reviewed. For plants, USDA (APHIS) would initially review a genetically modified plant to determine its plant pest potential, and FDA would initially review the genetic construct being inserted into an animal as a "new animal drug."

V. CONCLUSION

As the application of biotechnology progresses, it is clear that plants and animals can be transformed through genetic engineering to be not only sources of food, but also producers of a wide range of substances that have value as therapeutics, industrial chemicals and other high value products. The ability to introduce novel traits through genetic engineering increasingly will create plant and animal varieties for purposes never envisioned by legislators. Federal regulators responsible for reviewing the health, safety, and efficacy of transgenic organisms and their products will continue to face challenges using existing laws to effectively address those issues.

Appendix I
Additional References

OSTP Coordinated Framework Regulations:

Office of Science and Technology Policy. 1984. Proposal for a Coordinated Framework for Regulation of Biotechnology; Notice. 49 Fed. Reg. 50856 (December 31, 1984).

Office of Science and Technology Policy. 1985. Coordinated Framework for Regulation of Biotechnology; Establishment of the Biotechnology Science Coordinating Committee; Notice. 50 Fed. Reg. 47174 (November 14, 1985).

Office of Science and Technology Policy. 1986. Coordinated Framework for Regulation of Biotechnology; Announcement of Policy and Notice for Public Comment. 51 Fed. Reg. 23302 (June 26, 1986).

Council on Environmental Quality – Office of Science and Technology Policy, 2001: CEQ and OSTP Assessment: Case Studies of Environmental Regulations for Biotechnology (January, 2001).

FDA Biotechnology Regulations:

Department of Health and Human Services, Food and Drug Administration. 1992. Statement of Policy: Foods derived from new plant varieties; Notice. 57 Fed. Reg. 22984 (May 29, 1992).

Department of Health and Human Services, Food and Drug Administration. 2001. Premarket notice concerning bioengineered foods; (Proposed Rule. 66 Fed. Reg. 4706 (January 18, 2001).

EPA Biotechnology Regulations:

Environmental Protection Agency. 1994. Microbial Pesticides; Experimental Use Permits and Notifications. 59 Fed. Reg. 45600 (October 31, 1994).

Environmental Protection Agency. 1994. Plant-Pesticides subject to the Federal Insecticide, Fungicide, and Rodenticide Act; Proposed Rule. 59 Fed. Reg. 60496 (November 23, 1994).

Environmental Protection Agency. 1997. Microbial products of biotechnology; Final Regulation under the Toxic Substances control Act (Final Rule). 70 Fed. Reg. 17910 (April 11, 1997).

Environmental Protection Agency. 1997. Plant-Pesticides, Supplemental Notice; Proposed Rule. 62 Fed. Reg. 27142 (May 16, 1997).

Environmental Protection Agency. 2001. Plant-Incorporated Protectants; Final Rule and Proposed Rule. 66 Fed. Reg. 37772 (July 19, 2001).

USDA Biotechnology Regulations:

Department of Agriculture, Animal and Plant Health Inspection Service. 1987. Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests; Final Rule. 52 Fed. Reg. (June 16, 1987).

Department of Agriculture, Animal and Plant Health Inspection Service. 1993. Genetically engineered organisms and products; Notification Procedures for the introduction of certain regulated articles; and Petition for Non regulated Status Final Rule. 60 Fed. Reg. 17044 (March 31, 1993).

Department of Agriculture, Animal and Plant Health Inspection Service. 1997. Genetically Engineered Organisms and Products; Simplification of requirements and procedures for genetically engineered organisms; Final Rule. 62 Fed. Reg. 23945 (May 2, 1997).

Website Addresses for Federal Agencies with Biotechnology Regulatory Responsibilities or with Biotechnology Information:

www.aphis.usda.gov/biotech/OECD/usregs.htm

www.aphis.usda.gov/bbep

www.aphis.usda.gov/biotech

www.ers.usda.gov/topics/view.asp?T=101000
(list of papers done by the Economic Research Service on Production of Biotech Crops)

www.nbiap.vt.edu/cfdocs/fieldtests1.cfm
(USDA Field Release Data Base)

www.aphis.usda.gov/biotech/status.html
(USDA Status of Biotech Applications)

www.aphis.usda.gov/biotech/not_reg.html
(list of plants no longer regulated by APHIS)

www4.od.nih.gov/oba
(home page for the Office of Biotechnology Activities at NIH)

www4.od.nih.gov/oba/rdna.htm
(information on the NIH Guidelines and RAC activities)

Appendix II
Acronyms

APHIS	Animal and Plant Health Inspection Service (USDA)
CEQ	Council on Environmental Quality (Exec. Office of the President)
CVM	Center for Veterinary Medicine (FDA)
DSHEA	Dietary Supplement Health and Education Act
EA	Environmental Assessment
EIS	Environmental Impact Statement
EPA	Environmental Protection Agency
EUP	Experimental Use Permit (EPA)
EPIA	Egg Products Inspection Act
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FSIS	Food Safety and Inspection Service (USDA)
GMPs	Good Manufacturing Practices (FDA)
GRAS	Generally Recognized as Safe (FDA)
INAD	Investigational New Animal Drug application (FDA)
MCAN	Microbial Commercial Activity Notice (EPA)
MIA	Meat Inspection Act
NADA	New Animal Drug Application (FDA)
NIH	National Institutes of Health
OSTP	Office of Science and Technology Policy (Exec. Office of the President)
PBN	Premarket Biotechnology Notice (FDA)
PHSA	Public Health Service Act
PIP	Plant Incorporated Protectant (EPA)
PPA	Plant Protection Act
PPIA	Poultry Products Inspection Act
RAC	Recombinant DNA Advisory Committee (NIH)
rDNA	recombinant deoxyribonucleic acid
TERA	TSCA Experimental Release Application
TSCA	Toxic Substances Control Act
USDA	U.S. Dept. of Agriculture
VSTA	Virus Serum Toxin Act