ISSUES IN THE REGULATION

of genetically engineered

plants and animals

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Introduction

Over the last quarter century, the rapid development of modern biotechnology (see Figure 1.1) has led to the creation of new varieties of plants and animals containing novel traits that would be difficult or impossible to achieve through traditional breeding. Biotechnology is a powerful tool that has the potential to deliver many benefits. Products have been developed or are being developed that can improve the agronomic performance of food crops (such as delivering higher yields or increased disease resistance), provide new consumer benefits (such as healthier oils and vegetables with longer shelf lives), provide new ways to make valuable industrial and pharmaceutical chemicals in plants and animals, and deliver environmental benefits (such as a reduction in the use of pesticides). Regarding fish and livestock, biotechnology has the potential to improve animal health, reduce the costs of production, and improve the quality of food derived from these animals.

Scientific reviews have generally found that the risks posed by biotechnology products do not differ in kind from the risks posed by their conventionally produced counterparts (GAO 2002; NRC 1987). In some ways, genetic engineering is more precise than conventional breeding, because scientists know what genetic material is being introduced and generally understand the functions of the expressed proteins. However, genetic engineering greatly expands the range of genetic material available for modifying plants and animals. Genetic engineering can introduce substances into food that have never been in the food supply before, and can give plants and animals new traits that have not previously been introduced into specific environments.

Concerns have therefore been raised about the potential of genetic engineering to introduce new toxins and allergens into food and to reduce essential nutrients (FDA 1992). Concerns have also been raised about potential adverse effects on the environment from the introduction of novel genetic traits, which could inadvertently be passed on to related wild plants or animals, reducing biological diversity and disrupting ecological systems (NRC 2002b). Plants that have been engineered to express substances to repel pests have raised concerns due to their possible impact on organisms other than the targeted plant pests and the possibility that the pests may become resistant to the pesticidal substances over time (NRC 2000).

The question of how best to regulate genetically engineered (GE) food and other products of agricultural biotechnology has been debated for nearly as long as the technology has existed. Since 1986, biotechnology products have been regulated under a Coordinated Framework of laws administered primarily by three agencies—the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA).[1] The central premise of the Coordinated Framework was that the process of biotechnology itself poses no unique risks and that products engineered by biotechnology should therefore be regulated under the same laws as conventionally produced

1 The development and publication of the Coordinated Framework for Regulation of Biotechnology was led by the Office of Science and Technology Policy (OSTP) in the Executive Office of the President, but the Framework represented the cumulative positions of the key regulatory agencies (OSTP 1984 and 1986). Principles of the Coordinated Framework were further elaborated in subsequent OSTP-led reviews (OSTP 1990 and 1992).

Figure 1.1 A Note on Terminology

Terms relating to biotechnology are often used in a variety of ways and continue to evolve in their usage.

Biotechnology is a general term that refers broadly to the application of "biological systems in organisms to technical and industrial processes" (OSTP 1984). This broad definition encompasses techniques used for centuries, including traditional plant and animal breeding techniques and the use of microorganisms in fermentation and food processing, as well as the more modern biotechnology methods described below.

Modern biotechnology is generally defined as including techniques that involve the direct manipulation of genetic materials, including recombinant DNA (rDNA) techniques and cell fusion. The Codex Alimentarius Commission defines modern biotechnology to be the application of "(1) *in vitro* nucleic acid techniques, including [rDNA] and direct injection of nucleic acid into cells or organelles, or (2) the fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombinant barriers and that are not techniques used in traditional breeding and selection" (Codex Task Force 2002). Recombinant DNA technology generally involves the isolation and *in vitro* manipulation of discrete DNA segments containing the genetic material of interest and their insertion into a host organism. Guidelines of the National Institutes of Health define rDNA molecules as "either: (i) molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) molecules that result from the replication of those described in (i) above" (NIH 1994).

For simplicity's sake in this report, the term "biotechnology" generally means modern biotechnology. Also in this report, "agricultural biotechnology" refers to the use of modern biotechnology techniques, particularly rDNA techniques, to create new varieties of crops typically grown by farmers or livestock typically raised by ranchers, whether or not the crops or livestock are intended for food purposes.

The use of modern biotechnology to modify plants and animals is also often referred to as **genetic engineering.** New varieties of animals, plants, and microorganisms created through genetic engineering are referred to as being genetically engineered, bioengineered, or transgenic. The term **genetically modified** is technically imprecise since virtually all food has been modified on a genetic level by humans through selection and conventional breeding. Scientists prefer not to use the term, although it has gained widespread popular use in the media and is commonly understood to refer to modern biotechnology.

The term **risk** also requires elaboration. The fact that a product has the potential to create a risk does not mean that it is, in fact, harmful; rather, it means simply that its risk must be assessed. Risk includes both a hazard—something that has the potential to produce harm—and the likelihood of harm resulting from exposure to the hazard. Risk is therefore the product of two probabilities: the probability of exposure and the conditional probability of harm, given that exposure has occurred (NRC 2004).

products with similar compositions and intended uses. A second and no less important conclusion was that existing laws were adequate to meet regulatory needs.

Under the Coordinated Framework and related agency regulations, the first generation of genetically engineered crops has been introduced and commercialized. Today, a significant percentage of the corn, cotton, and soybeans in the United States is grown from genetically engineered varieties.[2] For the most part, this first generation of agricultural biotechnology products consists of single-gene, single-trait modifications made for agronomic purposes, primarily to make crops pest resistant or herbicide tolerant.

The adequacy of the Coordinated Framework has been a matter of disagreement from the beginning. Some have criticized the regulatory system in general (McGarity and Hansen 2001; *Alliance for Bio-Integrity et al. v. Shalala,* 116 F. Supp.2d 166 (D.D.C. 2000); Hansen 1999; Hopkins, Goldburg, and Hirsch 1991; Krimsky et al. 1989). Specific risk assessments and product approvals made by the agencies have also been the subject of criticism (NRC 2000, 120-125; UCS 1994). Others have argued that the regulatory system has worked well; they point to the absence of any evident food safety or environmental problems (NRC 2002b; Chassy et al. 2001; NRC 2000; Smith 2000) and the general scientific consensus that GE products are no riskier than their conventionally produced counterparts. Still others have argued that GE foods are over-regulated under the Coordinated Framework and should be afforded no greater review than conventional foods (Miller and Conko 2003).

The introduction of the first generation of GE crops did not occur without controversy. In Europe, the food safety crisis caused by "mad cow disease," while unrelated to GE food, raised broad concerns among EU consumers about the safety of the food supply and the competence of government regulators, contributing to widespread consumer wariness about GE food (Pringle 2003, 103). The resulting rejection of GE crops and market demand for non-GE varieties has become a major challenge for farmers, grain processors, grain shippers, food manufacturers, and others in industry (Shadid 2001; Shoemaker et al. 2001). Incidents in the United States have also illustrated the challenge of managing GE crops. In 2000, traces of StarLink, a GE variety of corn not approved for food use, were discovered in numerous food products. While the highly publicized incident caused no documented harm to human health, product recalls and trade disruptions cost industry hundreds of millions of dollars (Lueck 2000).

Today, biotechnology developers are poised to bring the next generation of agricultural biotechnology products to market (Monsanto 2003; PIFB 2001). (See Figure 1.2) While some new crop varieties will continue to deliver benefits primarily to farmers in the form of increased pest resistance or herbicide tolerance, others will represent a significant departure from the first generation. The next generation of GE crop varieties will likely include a wider range of desirable agronomic traits, including drought tolerance. Food crops may be modified with traits to improve freshness, taste, and nutrition. Plants could also be modified for nonfood purposes, such as the manufacture of pharmaceutical or industrial chemicals.

The next generation of agricultural biotechnology also includes animals. In some cases, transgenic animals could be modified to include traits that improve the production of

2 In 2002, genetically engineered varieties accounted for 81% of the soybeans, 73% of the cotton, and 40% of the corn grown in the United States (NASS 2002).

Figure 1.2 Possible "Next Generation" GE Products

- Crop plants that are salt tolerant, high in certain vitamins or minerals, high in protein, low in fat, less allergenic, higher yielding, or less susceptible to spoiling
- Plants that contain antibodies for use in diagnostic testing, biosensors capable of detecting landmines, vaccines, enzymes with industrial uses, epoxy oil for use in paint, plastic polymers, human proteins for use in therapeutics and diagnostics, or anticoagulants
- Trees that are disease or insect resistant or lower in lignin content (i.e., better for making paper)
- Turf grasses that are herbicide resistant or drought, salt, or cold tolerant
- Flowers that come in nontraditional colors, are longer-lived after cutting, or have stronger or longer stems
- Plants that can absorb high concentrations of hazardous metals, for use in environmental remediation
- Mammals that produce tissues or organs for human beings, proteins for medical therapies, or a material similar to spider silk
- Livestock that are disease resistant and thus require fewer antibiotics
- Farm-raised fish that are disease resistant, faster growing, cold tolerant, or sterile

food; examples include faster-growing fish and disease-resistant cattle. In other cases, animals will be modified to produce industrial or pharmaceutical products, and even to grow organs for human transplantation.

Many of these genetic modifications will be substantially more complex than the single-gene, single-trait modifications of the first generation of GE crops. The new products are expected to enter into the regulatory review process in the next two to ten years and could pose novel issues for the regulatory agencies.

When the federal agencies first proposed the Coordinated Framework nearly 20 years ago, they acknowledged the need to periodically reassess the regulatory system to ensure that it is keeping pace with the rapid development of the technology (OSTP 1984).[3] The impending introduction of the next generation of agricultural biotechnology products has led to a renewed interest in examining the adequacy of the current regulatory system for such future products.

In evaluating the adequacy of a regulatory system, the purposes of the system must initially be considered. The primary purpose of any regulatory system is to protect against

3 The agencies stated that "there are always potential problems and deficiencies in the regulatory apparatus in a fast-moving field," and they noted the need to monitor developments that might create "potential gaps in regulation" (OSTP 1984).

harm by assessing and managing the risks of potentially harmful products and activities. At the same time, a regulatory system should provide a clear pathway to the market for safe and useful products. Over the years, Congress has passed numerous laws to ensure the safety of food, drugs, pesticides, chemicals, and other substances that could pose risks to health or the environment. While the primary goal of a regulatory system is to prevent harm, the public trust generated by an effective and credible regulatory system also has considerable importance for commerce. Regulation can provide assurance to consumers that they can rely upon the agency's independent expertise and purchase products without concern. These commercial benefits can be lost, however, if consumers lack confidence in the integrity and competence of the regulatory system. For this reason, many interested parties, including the biotechnology industry, have consistently acknowledged the importance that a credible, rigorous regulatory system has in ensuring the market acceptance of its products.[4]

About This Report

This report reviews the existing regulatory system for biotechnology, identifies a number of issues and concerns relating to the adequacy of the system for future biotechnology products, and sets forth policy options and perspectives for addressing those concerns. In preparing this report, the Pew Initiative on Food and Biotechnology drew on a significant amount of analysis and information developed by experts for the Stakeholder Forum on Agricultural Biotechnology, a consensus-based dialogue process supported by the Initiative.[5] However, the analysis in this report represents solely the work of the staff of the Initiative, and does not reflect the views of the Forum nor any of its members.

The overarching policy question addressed in this report is whether the regulatory system is "good enough" to protect public health and the environment and to maintain public trust, in light of likely future technology trends. Interested parties have a range of opinions on that question. No regulatory system is perfect, and biotechnology is hardly the only area where issues have been raised about the adequacy or structure of the regulatory system.[6] Moreover, some of the issues raised about the regulatory system for agricultural biotechnology apply in other regulatory contexts, yet they have not generated as much interest or concern.[7]

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4 For example, the Grocery Manufacturers of America (GMA) said in a 1999 press release: "Confidence in our scientific regulatory standards has...been a pivotal factor in Americans' strong acceptance of biotechnology." Likewise, the Biotechnology Industry Organization (BIO) wrote in 2000: "The agricultural biotechnology industry is totally committed to developing safe and nutritious crops that are trusted and valued by consumers, farmers, and food companies. The FDA consultation process, together with the regulatory reviews conducted by EPA and USDA, are critical to establishing and maintaining this trust."

5 Appendix A contains a list of Stakeholder Forum members and the experts who contributed to the Forum process. While several current and former regulatory agency officials made presentations to the Stakeholder Forum, the Forum itself did not include any agency representatives as members.

6 Just as one example, the structure of the regulatory system for food safety in general has also been the subject of extensive critical comment (NRC 1998).

7 For example, scientific reviews have indicated that conventionally bred crop varieties can lead to some of the same types of environmental risks associated with genetically engineered varieties, yet there is little apparent interest in subjecting conventional crops to increased regulatory scrutiny (NRC 2002b, 86).

The intent of this report is to provide policy makers with a better understanding of some of the current debates about the U.S. regulatory system for agricultural biotechnology and about some of the policy options that are available, should change be desired. The report is not by any means a comprehensive review of the extensive public policy and legal literature related to biotechnology regulation, but rather a snapshot of current issues as informed by policy experts and the Stakeholder Forum process. The report does not make recommendations nor attempt to pass judgment on the significance of the issues or the desirability of any particular policy option. Included are arguments both for and against changing the system, as well as explanations of the advantages and disadvantages of options for making change, should change be desired.

The report focuses primarily on those aspects of the U.S. federal regulatory system that address food safety and environmental protection, and the report addresses policy options in the context of improving the current regulatory system of shared agency responsibilities. More dramatic options, such as establishing a single biotechnology agency, were not considered, primarily because they are less likely to be implemented. Other important legal and regulatory issues are simply beyond the scope of this report, including labeling and consumers' "right to know," animal welfare issues, state responsibilities, international regulations and trade issues, and economic liability and insurance issues arising from the inadvertent mixing of GE and non-GE crops. Similarly, the report does not tackle scientific controversies, although it notes recent scientific reviews by the National Academy of Sciences where appropriate. Finally, the report is not intended to be a substantive assessment of how well agencies have done in regulating individual agricultural biotechnology products, which would require an analysis beyond the scope of this report.[8]

Evaluating the adequacy of the regulatory system to assess and manage risk involves many factors. This report discusses at some length the legal authorities of the three main regulatory agencies. Legal authority is important because it addresses the questions of whether agencies will have sufficient authority to review future products before they go to market to prevent food safety and environmental problems, and whether they will have authority to detect and respond to any problems after products are already on the market. Adequate legal authority not only helps ensure that agencies have appropriate regulatory tools to assess and manage risk, but also helps to instill confidence in consumers that the regulatory system is working. The report also assesses the process by which agencies assess and manage risk, which has implications for public trust. Transparency, clarity, and public participation are elements of a regulatory system that contribute to public trust.

The Coordinated Framework for Biotechnology

Under the policies established in the 1986 Coordinated Framework, products developed by agricultural biotechnology are regulated under the same laws that govern the safety, efficacy, and environmental impacts of similar products derived by more traditional methods (OSTP 1986). Three federal agencies have the primary responsibility for regulating

8 Reports by the National Academy of Sciences' National Research Council on pest-protected plants (NRC 2000) and the environmental effects of transgenic plants (NRC 2002b) contain reviews of the EPA's and USDA's programs, respectively.

Table 1.1 Federal Laws Potentially Applicable to GE Organisms and Products Derived from Them

TITLE OF ACT	ABBREVIATION	AGENCY	CITE
The Federal Insecticide, Fungicide, and Rodenticide Act	FIFRA	EPA	7 USC § 136
The Toxic Substances Control Act	TSCA	EPA	15 USC § 2601
The Food, Drug, and Cosmetic Act	FDCA	FDA; EPA	21 USC § 301
The Plant Protection Act	PPA	USDA	7 USC § 7701
The Virus Serum Toxin Act	VSTA	USDA	21 USC § 151
The Animal Health Protection Act	AHPA	USDA	7 USC § 8031
The Federal Meat Inspection Act	FMIA	USDA	21 USC § 601
The Poultry Products Inspection Act	PPIA	USDA	21 USC § 451
The Egg Products Inspection Act	EPIA	USDA	21 USC § 1031
The Animal Damage Control Act	ADCA	USDA	7 USC § 426
The Animal Welfare Act	AWA	USDA	7 USC § 2131
The National Environmental Protection Act	NEPA	(All)	42 USC § 4321

GE organisms and products under at least ten different laws. The agencies are described below; the laws are listed in Table 1.1.

- **The U.S. Department of Agriculture.** The USDA is responsible for regulating potential agricultural plant pests and noxious weeds under the Plant Protection Act (PPA); for the safety of animal biologics under the Virus Serum Toxin Act (VSTA); for the safety of meat products under the Federal Meat Inspection Act (FMIA) and related laws; for controlling livestock diseases under the Animal Health Protection Act (AHPA); for ensuring the humane treatment of animals under the Animal Welfare Act (AWA); and for protecting livestock from injurious wildlife species under the Animal Damage Control Act (ADCA). Within the USDA, the Animal and Plant Health Inspection Service (APHIS) has the major responsibility for the regulation of GE organisms and products. The Food Safety and Inspection Service (FSIS) may also have a role to play.

- **The Food and Drug Administration.** The FDA is responsible for the safety of food and animal feed and for the safety and efficacy of human and animal drugs, biologics, and dietary supplements under the authority of the federal Food, Drug, and Cosmetic Act (FDCA). Within the FDA, four centers have responsibility for biotechnology products. The Center for Food Safety and Applied Nutrition (CFSAN) deals with the safety of food derived from genetically engineered crops. The Center for Veterinary Medicine (CVM) has publicly asserted its regulatory role with regard to genetically engineered animals. The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) are involved in the regulation of drugs and pharmaceutical products developed from GE crops and animals.

- **The Environmental Protection Agency.** The EPA is responsible for regulating pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Under FIFRA, the EPA ensures that pesticides pose no unreasonable risk to the environment. The EPA also sets allowable levels ("tolerances") or exemptions from tolerances for pesticide residues in food under the FDCA. In practice, the EPA regulates the pesticidal substances produced by some genetically engineered crops. The EPA also regulates certain nonpesticidal chemical substances, including genetically engineered microorganisms, under the Toxic Substances Control Act (TSCA).

The FDA, EPA, and USDA are also subject to the National Environmental Policy Act (NEPA), which requires all federal agencies to consider the consequences of their proposed actions on the environment prior to making decisions. NEPA outlines procedures for environmental review, but it does not require agencies to meet particular environmental standards before moving forward. If an agency must make a decision regarding an agricultural biotechnology product, the NEPA process may come into play.

As agricultural biotechnology 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 engineered to make their own pesticides presented the agencies with a product that was simultaneously a potential plant pest, a food, and a pesticide. This led the EPA to develop new regulations specifically applicable to "plant-incorporated protectants," or PIPs (40 CFR Parts 152 and 174). Thus, while there are no laws specific to biotechnology products, agencies have developed a number of regulations and guidelines that apply existing laws to biotechnology products to ensure appropriate regulatory oversight.

Which laws apply depends both on the nature of the organism and the intended use of the product. Table 1.2 provides a summary of the laws that apply to GE organisms. Transgenic plants are regulated by APHIS under the PPA to control "plant pests." The genetic modification of animals may be regulated by the FDA under the "new animal drug" provisions of the FDCA, although this area of regulation is not yet well developed. Transgenic livestock may also be regulated by APHIS under the AHPA and related statutes, but these authorities are not clear at this time. Transgenic microorganisms are regulated as "new chemical substances" under TSCA; transgenic micoorganisms that are plant pests would also be regulated by APHIS.

The properties and intended uses of products derived from genetically engineered plants, animals, or microorganisms can determine their regulatory pathways. (See Table 1.3) If a product is a plant-based food product, it is regulated by the FDA under the adulterated food provisions of the FDCA. Another product might be regulated as either a drug or a dietary supplement, depending on the producer's claims for the product. If it purports to cure a disease, it could constitute a "new drug" required to be approved by the FDA as safe and effective. If the claim is simply that it promotes some aspect of health, it could fall under the less-stringent requirements for dietary supplements. Pesticides produced in plants (i.e., PIPs) are regulated by the EPA under FIFRA and the FDCA to ensure environmental and public health. The EPA also may regulate certain substances produced by GE plants or animals under TSCA, as this law gives the agency authority to regulate new chemical substances or uses that could pose a risk of harm to human or environmental health.

Table 1.2 The Regulation of Genetically Engineered Organisms Under the Coordinated Framework *(uncertain areas in italics)*

GENETICALLY ENGINEERED ORGANISM	AGENCY	LAW
PLANTS		
All plants	USDA-APHIS	PPA
ANIMALS		
Animals (including fish)	*FDA*	*FDCA*
Livestock	*USDA*	*AHPA; ADCA*
MICROORGANISMS	EPA; USDA	TSCA; PPA

Table 1.3 The Regulation of Products Derived from Genetically Engineered Organisms *(uncertain areas in italics)*

GENETICALLY ENGINEERED PRODUCT	AGENCY	LAW
HUMAN FOOD		
Whole Foods		
Plants (i.e., vegetables, fruits)	FDA-CFSAN	FDCA
Meat, poultry, and eggs	USDA-FSIS *FDA-CVM*	FMIA; PPIA; EPIA *FDCA*
Fish	FDA-CVM	FDCA
Food Articles		
Food additives	FDA-CFSAN	FDCA
Dietary supplements	FDA-CFSAN	FDCA
ANIMAL FEED	FDA-CVM	FDCA
DRUGS AND BIOLOGICS		
Human drugs	FDA-CDER	FDCA
Human biologics	FDA-CBER	FDCA
Animal drugs	FDA-CVM	FDCA
Animal biologics	USDA-APHIS	VSTA
HIGH-VALUE PRODUCTS		
Cosmetics	FDA-CFSAN	FDCA
Pesticidal substances in plants (PIPs)	EPA	FIFRA
Other new chemical substances	EPA	TSCA

While the policy remains that genetically engineered products should receive the same regulatory treatment as similar, conventionally produced products (OSTP 1986), in practice agencies have developed a hybrid system that effectively treats biotechnology products differently. In part, this evolution has resulted from the difficulty of fitting biotechnology products into pre-existing legal categories, as in the case of PIPs, and in part due to the perceived public interest in affording GE products greater scrutiny. For example, the USDA's rules requiring notification and permitting for field trials of genetically engineered plants rest almost entirely on the process by which the plants are genetically engineered (7 CFR § 340.1). New varieties of plants created through conventional breeding require no similar regulatory scrutiny, although the USDA could take action against any plant that turned out to be a plant pest. Similarly, the FDA's policy of encouraging biotechnology companies to submit safety data prior to marketing food from a new GE crop variety (FDA 1992 and 1997a) effectively applies a higher level of regulatory scrutiny to genetically engineered crops than to conventionally bred crops. (The FDA has proposed making this consultation process mandatory (2001a), but the proposal has not been made final.) New varieties of fish bred for aquaculture do not require prior FDA approval, unless they are created through genetic engineering (CEQ and OSTP 2001). As a practical matter, the bright line between *process* and *product* has become substantially more difficult to draw, and thus the distinction has become less useful.

Evaluating the Current Regulatory System: General Issues

In any kind of evaluation, it is helpful to assess the subject at hand against clear criteria. This report employs four criteria to assess the current regulatory system governing agricultural biotechnology and to determine if any of the proposed policy options would improve the system or not. The criteria include: overall responsibility and legal authority; pre-market authority; post-market authority; and clarity, transparency, and public participation. The issue of coordination is also mentioned here, as it is discussed in Chapters 4 and 5.

This section describes each of these criteria and explains the concerns or controversies that have arisen in each area with regard to agricultural biotechnology.

OVERALL RESPONSIBILITY AND LEGAL AUTHORITY

An initial criterion for an effective regulatory system is that regulatory agencies should have clear legal jurisdiction and authority over all products and activities that may pose a risk to human health or the environment. Clear responsibility and legal authority is important not only for ensuring the protection of health and the environment, but also for providing the public and technology developers with a clear understanding of the regulatory pathway to market. A product should not fall through the regulatory cracks because no agency has clear jurisdiction or authority. Similarly, if a product could come under the authority of one or more agencies, the agencies need to coordinate those authorities to make their respective responsibilities clear and to function in a way that is not overly burdensome.

As noted previously, no law specifically addresses biotechnology. The laws on which the agencies rely for their regulatory authority over biotechnology products are more general laws, usually enacted for other purposes. As needed, regulators have interpreted their authority in creative ways to ensure that all new agricultural biotechnology products are

reviewed. The FDA, USDA, and EPA have all issued guidelines and regulations as necessary to clarify the application of the existing laws to specific products of biotechnology.[9] This approach has enabled agencies to cover all of the agricultural biotechnology products brought to market to date.

The use of existing, general laws to regulate biotechnology raises two issues. First, while agencies have issued regulations and guidances based on their interpretations of their authority to cover biotechnology products developed thus far, some of those interpretations may be legally questionable. Second, agencies have not yet provided guidance on how they will regulate some new, forthcoming products of biotechnology under existing laws. Biotechnology can be used to create new products that do not fit neatly within existing product definitions, which rely on old laws that clearly never anticipated modern genetic engineering techniques. Fitting some of the new products into existing legal frameworks may prove to be legally challenging.

It is not uncommon for agencies to apply laws to situations or products that were not expressly anticipated when the laws were written, and courts often give deference to agencies' interpretations of their own laws. In the case of laws intended to protect the public health, courts have often supported agencies' broad interpretations of Congressional intent.[10] However, legal room for agency creativity is not boundless. Agencies cannot exercise authority beyond that delegated by Congress, and actions beyond that authority can be struck down by the courts if challenged.[11]

Whether these legal uncertainties are significant from a policy perspective is subject to opinion. On the one hand, to the extent that no one challenges an agency's assertion of its authority and all parties comply with its requirements, legal uncertainties may have little practical effect. For example, developers of genetically engineered crops routinely consult with the FDA on a voluntary basis because of the practical marketplace reality that buyers would penalize products that had not been through the FDA's consultation process. Technology developers are unlikely to challenge a regulatory agency, because they obtain market benefits from having a regulatory review or approval.

On the other hand, if a legal challenge or enforcement issue does arise, a court could set aside an agency's action as unlawful, potentially leaving the agency without a legal basis for regulating biotechnology products. In addition, as a policy matter, some believe

9 For example, the EPA has issued regulations applying FIFRA to plant-incorporated protectants (40 CFR Parts 152 and 174) and applying TSCA to genetically engineered microbes (40 CFR Parts 700, 720, 721, 723 and 725); the USDA has issued regulations covering genetically engineered plants (7 CFR Part 340); and the FDA has issued guidance on foods derived from genetically engineered crops (FDA 1992).

10 In *United States v. Article of Drug...Bacto-Unidisk,* for example, Chief Justice Earl Warren observed that the FDCA is remedial legislation that needs "to be given a liberal construction consistent with...[its] overriding purpose to protect the public health...." (89 S. Ct. 410, 418 (1969)). Similarly, Justice Felix Frankfurter observed in *United States v. Dotterweich* that the FDCA touches the lives and health of people who, in the circumstances of modern industrialism, are largely beyond self protection and that, consequently, regard for these purposes "should infuse construction of the legislation if it is to be treated as a working instrument of government and not merely as a collection of English words" (64 S. Ct. 134, 136).

11 See, for example, *Food and Drug Administration v. Brown & Williamson Tobacco Co.,* 529 U.S. 120 (2000). Many legal scholars believe that courts are subjecting broad agency interpretations to increasing judicial scrutiny and are less likely to defer to agency determinations.

it is inappropriate for agencies to stretch their regulatory authority into areas beyond those clearly contemplated by Congress. Others also argue that a regulatory system that effectively depends upon the voluntary cooperation of those subject to the regulation is unlikely to be viewed as credible. Therefore, the market benefit of regulatory review could be diminished by a lack of credibility in the review process.

An additional issue is that the agencies have yet to clearly indicate how (or whether) they will regulate some future biotechnology products. In a number of cases, a product might fall under more than one product category, and therefore under more than one law.[12] This creates a coordination problem and the potential for stifling product approvals. Also, the choice of law under which to regulate a product will have significant implications for the rigor and transparency of its regulatory review. As noted in the following section, different laws provide different powers and procedures to different agencies.

Even where a biotechnology product falls clearly within the jurisdiction of a particular agency and law, the law may give the agency authority over only a limited set of risks. For existing biotechnology products, agencies have responded to these limitations by coordinating their regulatory review functions (OSTP 1986). So, for example, with respect to a crop that has been engineered to produce a pesticidal substance, the EPA has responsibility for assessing and managing the environmental and food safety risks of the pesticidal substance, the FDA has responsibility for assessing other food safety risks (and enforcing the EPA's food safety decision), and the USDA has responsibility for assessing and managing plant pest and other environmental risks other than those posed by the pesticidal substance. In some cases, however, particularly for some new biotechnology products, it is not clear whether any one agency or any group of agencies will have clear legal authority to look at the full range of potential risks posed by the product.

PRE-MARKET AUTHORITY

Pre-market authority refers to a regulatory agency's ability to assess and approve a product's health and environmental safety *before* it goes to market, to prevent problems before they occur. Because different laws governing biotechnology were enacted at different times and for different purposes, the degree of pre-market authority given to the agencies under these laws varies widely. Some laws presume that certain substances—such as drugs, plant and animal pests and diseases, food additives, and pesticides—inherently pose risks to human health or the environment. These laws therefore provide authority for regulatory agencies to prevent the introduction of these substances into commerce without prior review and approval. Under these laws, it is unlawful to take a product to market without

12 For example, many laws define products to be governed by the law according to their intended use (e.g., FIFRA (7 USC § 136(u)) and the FDCA (21 USC § 321(v))). That is, a given substance may be regulated as an industrial chemical, a drug, or a food additive (or some other product) depending on its intended use. In each case it would be regulated by a different federal agency under different statutory requirements. But the issue is further complicated when the means of manufacturing the substance is through a genetically engineered plant or animal. For example, a chemical intended to be used as a new human or animal drug has to be approved by the FDA. But does a food crop genetically engineered to produce the drug in its tissues become a "drug manufacturing facility" for the purposes of FDA coverage? Or does the FDA become involved only after the crop has been harvested and the drug extracted? Does the FDA have authority if the grower has no intention of extracting the chemical and using it as a drug? These questions remain to be clearly answered.

the required agency approval. Generally speaking, the burden is on the developer to prove that such a product is safe for its intended use. For other products that have a long and safe history of use (e.g., food and new crop varieties), the laws generally provide authority for agencies to act only after there is a reasonable likelihood of harm. In these cases, the burden is on the government to show that a product is or may be harmful in order to remove it from the market. Therefore, some biotechnology products are reviewed under mandatory pre-market approval laws, while others may legally move to market without any prior agency notification, review, or approval. (See Table 1.4.)

Biotechnology products that require a mandatory pre-market approval include PIPs (which are regulated as pesticides by the EPA), human and animal drugs (FDA), plant pests (USDA), and food additives (FDA). Under the laws regulating those products, manufacturers bear the burden of proving to the agencies' satisfaction that products meet the appropriate legal standards. New food products (conventional or GE) and conventionally bred new varieties of crops, by contrast, may legally move to market without any prior agency review for food safety. New chemicals must be reviewed by the EPA through a mandatory pre-market notification process before going to market, but, unlike with the above laws, the burden in that case is on the EPA to demonstrate that a product may pose an unreasonable risk.

The application of different regulatory review processes to different biotechnology products raises several issues. In some instances, products that present similar risks may receive different regulatory treatment.[13] In addition, the lack of a mandatory pre-market approval process for most foods derived from genetically engineered crops has raised concerns about the adequacy of that process to ensure food safety (CSPI 2001). Some have noted the apparent inconsistency in a regulatory system that requires a mandatory pre-market approval to ensure that plants will not be injured but does not require a similar mandatory pre-market approval to ensure that food is safe to eat (Foreman 2004). Others would respond that such outcomes are the simply the result of assessing risks on a product-by-product basis, and that the system ensures food safety in practice.

Finally, the way that a biotechnology product is defined affects the regulatory treatment it receives. For example, if a substance added to a food via genetic modification is novel or differs in some significant way from substances already found in food, the FDA is likely to treat it as a "food additive." A developer has the burden to prove, in a potentially lengthy food additive approval rulemaking, that the food additive poses a "reasonable certainty of no harm" before it can legally be sold (21 CFR § 170.3(i)). In contrast, if a substance added to a food from genetic engineering is substantially similar to substances already in food, the FDA presumes it is "generally recognized as safe" (GRAS), and the developer may legally take it to market without the FDA's prior review or approval (FDA 1992 and 2001a). Thus, faced with two very different regulatory tracks, one of which could delay the introduction of a product for years, developers of biotechnology crops have every incentive to

13 As discussed in more detail in the following chapters, to date, foods derived from herbicide-tolerant crops have been considered to be as safe as comparable foods and therefore have gone to market without a mandatory pre-market food safety approval (FDA 1992). In contrast, insect-resistant crops must be approved by the EPA as safe to eat under a mandatory pre-market approval process for pesticide residues in food (40 CFR Part 174). Likewise, while a pre-market food safety approval is not required for foods from GE crops (excepting those containing pesticidal substances) (FDA 1992), the FDA has proposed requiring a pre-market approval for the safety of food from transgenic animals (CEQ and OSTP 2001).

Table 1.4 Differences in the Regulation of GE Products

SELECTED GE PRODUCTS	LEGAL CATEGORY	MANDATORY PRE-MARKET NOTIFICATION	MANDATORY PRE-MARKET APPROVAL	LEGAL STANDARD	BURDEN OF PROOF
Pesticidal substances added to food crops through genetic engineering	Plant-incorporated protectant (pesticide)	Yes	Yes	No unreasonable adverse effects on environment; reasonable certainty of no harm for pesticide residues in food	Developer (for approval)
Substances added to food or feed that are substantially equivalent to substances found in food	"Generally recognized as safe" substance	No[a]	No	General recognition among experts based on history or scientific tests that the substance is safe	FDA (in enforcement)[b]
Nonpesticidal substances added to food that are not substantially equivalent to substances in food and that are not generally recognized as safe	Food additive	Yes	Yes	Reasonable certainty of no harm	Developer (for approval)
Whole foods that are substantially equivalent to their comparable counterparts	Food or feed	No[a]	No	"As safe as" conventional food	FDA (in enforcement)[b]
Livestock and fish	New animal drug	Yes	Yes	Safe and effective for the animal; reasonable certainty of no harm from drug residues in food	Developer (for approval)
Plants, animals, and microorganisms (regardless of purpose)	Plant pest	Yes	Yes[c]	May injure, damage, or cause disease in any plant or plant product	Developer (for approval)
Microorganisms	New chemical substance	Yes	No[d]	No unreasonable adverse effects on environment	EPA[d]

a. The FDA has proposed a mandatory notification requirement for bioengineered foods, but the proposal has not been made final (2001a). The FDA encourages developers to voluntarily consult with the agency before bringing a GE food product to market (1997a).

b. In an enforcement proceeding, the burden would be on the FDA to show that the marketing of the product violated the FDCA. For whole foods, the FDA would need to show a reasonable possibility of harm; for added substances, the FDA would need to show that the substance was an unapproved food additive, and therefore not generally recognized as safe.

c. In some cases it may be possible to commercialize a GE plant under a field trial notification process, which does not involve a formal agency approval.

d. Pre-market notification is mandatory under Section 5 of TSCA, but a new chemical substance may go to market unless the EPA finds that the product poses an unreasonable risk.

characterize new products as GRAS, and to avoid developing products that might trigger the food additive process.

POST-MARKET AUTHORITY

Post-market authority refers to an agency's authority to monitor products and respond to any problems after a product has entered the marketplace. There are several reasons why agencies might need to monitor biotechnology products after they have been approved. In some cases, agencies want to be certain that manufacturers and growers are complying with any restrictions the agencies have imposed on products in order to ensure their safe use. In several recent instances, failure to follow agency restrictions has led to costly problems. As mentioned previously, a genetically engineered variety of corn called StarLink, which had been approved solely for animal feed, was found in 2000 by an environmental advocacy group to have entered the human food supply. While no human health risk arising from the error was demonstrated, food manufacturers were forced to recall products that contained small amounts of StarLink, and international trade was disrupted (Taylor and Tick 2003). In 2002, contrary to USDA guidance, some volunteer plants left over from a field trial of corn genetically engineered to produce a pharmaceutical chemical became mixed in with some soybeans that were later grown on the same field. The problem was detected by the USDA before the soybeans, mixed with residues of the pharmaceutical corn, left the grain elevator and entered the food supply (USDA 2002).

It is also important for agencies to monitor the use of biotechnology products to ensure that no unanticipated adverse effects occur, and to confirm that any restrictions are working as expected. Such post-approval monitoring is particularly important where information available at the time of approval is limited or uncertain. For example, the EPA has required farmers to plant a portion of their fields with corn and cotton that has not been bioengineered with *Bacillus thuringiensis* (*Bt)* genes (which have pesticidal properties), to try to prevent the development of *Bt*-resistant insect pests (EPA 2001b). At the time of the approval, there was scientific disagreement about how much corn needed to be set aside for non-*Bt* varieties (EPA FIFRA SAP 2002). As a result, it is important for the EPA to be able to monitor not only compliance with the restrictions, but the development of *Bt* resistance among insects to see whether the restrictions are working as expected.

Finally, agencies need to have authority to act in the event that problems are discovered. Products can sometimes raise unforeseen issues after they have been introduced into the market, despite the most careful regulatory review. For example, after the EPA approved *Bt* corn, a study suggested that Monarch butterfly larvae might be killed by exposure to *Bt* corn pollen (PIFB 2002). The EPA was able to order a "data call-in" to require additional studies to be done, which largely showed that exposures in real-world conditions were likely not to cause much harm (EPA 2001a). Agencies need to be aware of unexpected events to be able to respond with appropriate risk management actions.

The laws under which the agencies regulate agricultural biotechnology have different legal authorities to impose post-approval restrictions, to monitor for compliance and unanticipated effects, and to respond to problems that might emerge. Some agencies have fairly broad powers to require monitoring or reporting once a product goes to market, while other agencies are much more restricted in what they can do once a product is on the market. In general, agencies have more post-market authority over products that are presumed

to present some risk, and less over products that traditionally have a history of safe use or are, if novel, presumed to pose no risk. Table 1.5 summarizes the post-market treatment of various GE products.

If a product is a plant that has been genetically engineered to produce a pesticide, the EPA can use its authority under the pesticide laws to impose restrictions on its use in order to ensure that it does not harm the environment or threaten food safety. If violations of those restrictions occur, the EPA can revoke the registration (i.e., the license to sell the pesticide) and impose penalties. The EPA can also require the manufacturer to monitor and provide data, and to report any unanticipated or adverse effects. The pesticide laws are an example of a regulatory regime that gives an agency fairly extensive powers to detect and respond to any problems once a product has been approved.

Other agencies have more limited authorities. New food products that are "generally recognized as safe" can legally go directly to market without prior FDA approval. The FDA does not track such products and may not know whether they are being sold. The FDA can take action only after a problem has been discovered, and then it must act in an enforcement proceeding and prove that the food product is "adulterated," or unsafe for human use (21 USC § 342). (In practice, the FDA often can achieve informal enforcement without resorting to a formal enforcement action, since food makers and retailers are unlikely to want the adverse publicity of an FDA enforcement action.)

A genetically engineered crop that is a potential plant pest is reviewed and approved by APHIS prior to field trials and commercial release, to ensure that the plant will not injure crops nor pose unreasonable risks to the environment. In most cases, however, once APHIS has been satisfied on those points, it determines that the crop is not a plant pest and permits it to be grown commercially without restrictions. By finding that the crop is not a plant pest, APHIS "deregulates" the plant—that is, the plant is no longer subject to APHIS's legal authority. APHIS has no authority to monitor a deregulated GE crop after it has gone to market, and the manufacturer has no legal obligation to monitor or report unanticipated problems. Should a problem occur, APHIS would have to have new evidence showing that the previously deregulated crop was indeed a plant pest in order to take action.

CLARITY, TRANSPARENCY, AND PUBLIC PARTICIPATION

Clarity, transparency, and public participation are related criteria for assessing a regulatory system. They deal not with the substantive outcome of regulatory decisions, but with the processes by which those decisions are made. Process is important not only because it can affect substantive decisions, but because it affects both public trust in the regulatory system and the credibility—and ultimate acceptance—of agency decisions. According the National Academy of Sciences' National Research Council, research indicates that "public confidence in environmental policy making is particularly sensitive to the opportunity for concerned citizens to be involved in the decision-making process" (NRC 2002b, 168). Also, if an agency's processes lack clarity, certainty, and predictability, businesses may not understand what is required for them to bring a product through the regulatory process and to market.

Transparency is the degree to which the basis of an agency's decisions is open for public scrutiny. Disclosure of both the critical data that an agency relies upon, as well as the agency's rationale for its decisions, helps to ensure the soundness of agency decisions by

Table 1.5 Post-Market Regulatory Treatment of Different GE Products

GENETICALLY ENGINEERED PRODUCT	LEGAL CATEGORY	POST-MARKET USE RESTRICTIONS	POST-MARKET MONITORING OR ADVERSE-EVENT REPORTING
Pesticidal substance added to plant	Plant-incorporated protectant (pesticide)	Yes	Yes
Substances in food "generally recognized as safe"	GRAS substance	No	No[a]
Non-GRAS substances in food	Food additive	Yes	Maybe[b]
Whole foods that are substantially equivalent to non-GE counterpart	Food or feed	No	No[a]
Livestock and fish	New animal drug	Yes	Yes
Plants under APHIS permit	Plant pest	Yes	Yes
"Deregulated" GE plants	None	No	No

a. The FDA has the authority to inspect and test under FDCA § 704.

b. The FDA has negotiated agreements for monitoring and reporting, but it is uncertain whether it has the legal authority to require them for food additives.

subjecting them to public review and ensures the integrity of the process by disclosing critical information the agency relied upon. Although it is most helpful if this disclosure comes before a final decision is made, disclosure after the fact can act as an important check on agency action, particularly if the case can be made that the action was arbitrary or not scientifically sound.

Clarity is related to transparency. A clear public description of the decision-making process, including what information the agency will require and what legal standard the agency will apply, helps the public and the regulated community understand the rules under which a product will be reviewed. If the regulatory process is uncertain, unpredictable, or unclear, the regulated community has a hard time making informed decisions and understanding in advance what the government will require in order to approve a new product, thereby hindering investment and innovation. Similarly, a lack of clarity about the process makes it difficult for the public to know in advance the rules that the government will follow in making its determinations. This could jeopardize the credibility of government decisions.

Public participation can take a number of forms, but the key element is an opportunity for the public to comment on pending decisions before they are made. Participation helps to ensure the openness and integrity of the regulatory process and can provide the public with a means to correct or supplement the data upon which the government is relying. If taken to an extreme, however, public participation can be unduly onerous and could bring a regulatory process to a halt.

Each of the agencies with responsibility for regulating biotechnology products operates under statutes that offer differing opportunities for transparency, clarity, and public participation. On one end of the spectrum, the new animal drug approval process that the FDA could use to approve GE animals provides no opportunity for public participation and little transparency. The FDA cannot disclose even the existence of an application for approval; instead, an explanation of the FDA's decision, along with a summary of the information relied upon, will be published after the FDA approves an application (21 CFR § 514.11(e)). To date, the FDA has not published any public guidance on what information it might use to evaluate the potential environmental impacts of such animals.

At the other end of the spectrum, the EPA's approval process under FIFRA is relatively transparent and provides opportunities for public comment prior to the agency's final decisions. With the cooperation of technology companies, the EPA makes available for public inspection much of the information submitted by the manufacturer, including health and safety data. Also, the EPA has published guidance on what information it will use, and the standard that it will apply, in making determinations about PIPs (40 CFR § 174.9). Transparency is not absolute, of course; agencies are prohibited from disclosing trade secrets and confidential business information (18 USC § 1905). However, agencies sometimes differ on the extent to which they are willing to defer to broad assertions of confidentiality (NRC 2002b, 177; NRC 2000, 176).

COORDINATION

Coordination refers to the way in which agencies with potentially overlapping jurisdictions work together, in order to minimize redundancies. Clearly, a regulatory system should avoid needless duplication. While efforts have been made by each administration to ensure a more coordinated system for biotechnology, the development of new varieties of genetically engineered organisms, combined with the vague boundaries of current law, have inevitably led to some duplication of regulatory effort. Both the EPA and APHIS must review GE plants modified to express pesticidal substances, for example, and each requires data from companies that are similar but not identical (NRC 2000, 162-165). Because each statute has its own process and legal standards, the same product is likely to be subject to the scrutiny of more than one agency. In addition to duplication and delay, the lack of coordination can sometimes result in gaps where it is unclear which agency has lead responsibility.

Rationales For and Against Changing the Current System

Different parties hold differing views about the significance of the concerns mentioned regarding the regulatory system governing agricultural biotechnology. Some experts argue against the need for change at this time, while others argue that change is needed. Those who believe changes are necessary are not of one mind either—they hold differing views about how to accomplish it. This section lays out the main arguments in the debate over these issues. *The arguments described herein do not necessarily reflect the opinions of the authors; rather, they are intended to represent a summary of the current debate as informed by experts and the Stakeholder Forum process.* To denote this change in "voice," the arguments are set in italics.

ARGUMENTS AGAINST CHANGE

The following are the primary arguments against changing the current regulatory system.

While any system can be improved, the current regulatory system for biotechnology products works well, and changing the system would likely generate more problems than it would solve. The current system, while not perfect, has proven to be flexible enough to respond to needs as they have arisen and can continue to adapt to meet future challenges.

To date, the regulatory system has subjected all field trials and general releases of genetically engineered plants to some level of review by a regulatory agency. No instance has been reported of a GE plant that has been field tested or grown commercially without following the appropriate regulatory review process. While several well-publicized compliance issues have arisen, compliance problems can crop up in any regulatory system, and in these cases the federal agencies responded quickly to avoid any possible harm.

The adequacy and effectiveness of the current system is demonstrated by the lack of any evidence of harm to human health or the environment from GE crops, despite the widespread introduction of these crops over thousands of acres in the United States. The National Research Council's recent reviews of PIPs and genetically engineered plants affirm the lack of any evidence of harm caused by those products (NRC 2000 and 2002b).

The concerns about inadequate or uncertain authority in the current system and coverage of future genetically engineered plants and animals are not significant. Agencies have sufficient flexibility in their laws to reach all biotechnology products that might raise concerns. Uncertainty and possible duplication can be clarified through agency policy guidance. While agencies may have to creatively and expansively interpret their legal authority to reach some biotechnology products, the risk that these interpretations will be successfully challenged—and that some products might go unregulated—is actually very low. As a practical matter, technology developers are unlikely to challenge an agency's questionable assertion of jurisdiction over its GE products, out of concern that the marketplace will reject a product if an agency claims that the developer has evaded a review or approval process.

Changing the regulatory system could be interpreted as an admission that the genetically engineered crops already on the market are unsafe, or that their safety has not been sufficiently proven. Given the on-going controversies over regulation and trade, overseas trading partners could latch on to this argument as a justification for further restrictions on genetically engineered crops.[14]

There is no scientific justification for changing the regulatory system. Scientific advisory groups continue to affirm that the process of biotechnology itself poses no inherent or unique risks, and there is no particular reason to single out products produced through biotechnology for a higher level of scrutiny. To the extent that some justification exists for a higher level of scrutiny of food products that contain novel proteins or unusual changes in toxicity, composition, or nutrition, those arguments apply equally to new varieties produced through conventional breeding, which have never required pre-market regulatory scrutiny.

14 Corn growers have estimated the cost of lost sales to the European Union (EU) due to its moratorium on GE plant approvals at $300 million a year (NCGA 2003a). The Bush Administration has filed a complaint at the World Trade Organization against the EU for its trade practices (Williams 2003).

Also, change is not needed to ensure confidence in the regulatory system. Public opinion polls consistently demonstrate a high level of public confidence in the FDA and in the safety of the food supply (PIFB 2003).[15] *There is little evidence to suggest that consumers are concerned about the safety of food from GE plants or the adequacy of the regulatory system. It could even be argued that the purpose of regulation is to assess and manage risks on the basis of science, and that creating public trust in the regulatory system is not an appropriate purpose for the regulatory system.*

Further, changes in the regulatory system can impose significant costs, both intended and unintended. To the extent that the regulatory system requires more data or more comprehensive reviews, the cost of bringing a product through the system will increase. Increased regulatory costs will raise a barrier to bringing products to market that may have significant economic, health, and environmental benefits. In addition, changes create costly uncertainty. Until new rules are fully developed, biotechnology product reviews would be delayed or hindered by the need to resolve the new legal questions that would inevitably arise. Thus, the costs of changing the regulatory system must be weighed against any of the purported benefits.

ARGUMENTS FOR CHANGE

The following are the primary arguments for changing the existing regulatory system. As with the above section, the opinions expressed in this section do not necessarily represent those of the authors, but rather reflect their understanding of the views held by proponents of these opinions.

The regulatory system needs to be improved in order to catch up with the technology, and a failure to do so could not only pose human health and environmental risks, but undermine public trust in the regulatory system and jeopardize market acceptance of agricultural biotechnology. The gaps and inadequacies in the current system are becoming increasingly apparent with the development of new biotechnology products that do not fit into the system.

Despite some regulatory mishaps in the first generation of agricultural biotechnology products,[16] *the crops currently approved for growing in the U.S. are unlikely to raise significant human health or environmental problems.*[17] *The main concern is the next generation of*

15 According to this consumer opinion poll, 83% of Americans surveyed trust the FDA when it comes to information about genetically engineered foods.

16 Critics of the current system point to the StarLink corn situation, in which the EPA refused to approve the product for food because of concerns about its potential allergenicity. The case showed both the weakness of the current science in predicting the allergenic properties of some GE foods, as well as the EPA's and FDA's failure to monitor compliance in the marketplace (Taylor and Tick 2003; Bucchini and Goldman 2002). The controversy over the possible effects of Bt corn on monarch butterflies also suggested a weakness in the EPA's regulatory review, according to some. While subsequent research indicated that the impact was negligible, one variety of Bt corn (which had already been taken off the market) was found to express higher levels of the pesticidal protein, which could have harmed monarch larvae (PIFB 2002).

17 While most observers acknowledge the lack of evidence of human health or environmental harm from crops introduced to date, they also question whether there have been systematic, scientific efforts to look for such harm. In one recent National Research Council report, the panel said that the conclusion that there were no environmental effects from the large-scale planting of commercial GE crops was "nonscientific," since "there has been no environmental monitoring" of the crops. "The absence of evidence of an effect is not evidence of absence of an effect," the panel said (NRC 2002b, 79).

products, which is likely to introduce more complex genetic modifications and multiple traits in comparison to the first generation, as well as being applied to a greater range of plants and animals. Many of these new and more complex applications will bring benefits but also raise novel and possibly more difficult regulatory issues.

The current system, which has already been stretched to cover current crops, is not likely to be adequate for dealing with the next generation of agricultural biotechnology products. Current legal authorities are not sufficient to cover certain new kinds of products and do not give agencies adequate tools to assess risk and prevent harm or to detect and respond to harm should it occur. The lack of an affirmative pre-market food safety approval process for most GE foods is an example of inadequate legal authority. Where agencies have used expansive and creative interpretations of their authority to cover biotechnology products, agencies are vulnerable to court challenges, particularly if a company or an importer wanted to get a product to market more quickly than its more responsible competitors. Review that relies upon voluntary compliance is inadequate to protect public health and the environment from those who might challenge the system.

Moreover, stretching an agency's authority through creative legal interpretations can strain credibility and trust in the system. Treating a GE crop as a "plant pest," the genetic modification of a fish as a "new animal drug," a GE animal as a "drug manufacturing facility," and a substance in a corn plant as a "pesticide" makes it difficult for the public to understand how regulatory decisions are being made. Credibility is also challenged when a regulatory system depends on voluntary compliance by the industry. When the processes that the agencies use to make decisions are not fully transparent and where there are no or limited opportunities for public participation, public trust in the regulatory system is further open to question.

Trust in government regulators is a critical component to build market acceptance of a new technology. Consumers must have confidence that new food products are safe to eat and pose no unreasonable environmental risks. The European experience with "mad cow disease" graphically illustrates the consequences of a collapse of confidence in government regulators and science. Whether the next generation of agricultural biotechnology products will be accepted by the marketplace will depend in part on a sound regulatory system that consumers trust. While consumers may currently trust the FDA and other regulatory agencies, polls continue to show that many consumers have concerns about biotechnology and that attitudes could harden against the technology quickly in the event of a crisis (PIFB 2003).[18]

Further, the legal uncertainties embedded in the current system make it difficult for companies to understand what the regulatory process will require and therefore to make informed choices about the investment of resources in the development and testing of new products. Legal uncertainty imposes costs and risks on industry. For example, under the FDA's current guidance, it is difficult to know in advance whether a new genetically engineered food could be brought to market relatively quickly under the voluntary notification program, or whether

18 In this poll, 25% believed that GE foods are "basically unsafe," while 48% said they did not know or did not have an opinion; 48% also reported being "opposed" to the introduction of GE foods in the U.S. market. At the same time, 89% of those polled agreed that the FDA should approve GE foods as safe before coming to market.

it will require a lengthy and costly food additive approval proceeding. Similarly, unresolved issues about what laws will be, or should be, used to regulate GE animals and some GE plants and plant products will hinder the commercialization and use of these products.

Many who support changing the system agree with most scientists that biotechnology does not pose unique risks, in the sense that traditional breeding techniques can result in similar types of food safety or environmental risks. However, we have extensive experience with traditional breeding and we know from such experience that such risks are quite low. In contrast, we have little experience with bioengineered products, and the ability of biotechnology to introduce totally novel proteins to food or new traits to the environment argues for treating biotechnology products as a class more cautiously than conventionally bred foods. Until more experience is gained with particular genetic constructs, all new biotechnology products should be subjected to some pre-market scrutiny for potential food safety and environmental risks, but the level of scrutiny should be proportionate to the potential risks.

Failure to change the regulatory system also carries risk. To the extent the system may not prevent or be able to quickly respond to unanticipated problems, the next crisis could be one that turns consumers against the technology. Those who argue for the status quo are betting that the current system will be able to adequately handle the challenges of more complex biotechnology products. A successful legal challenge could strike down the system and cause regulatory chaos. As a result, market acceptance of the technology could falter without greater assurance from regulators that the products pose no food safety or environmental risks.

As to international acceptance, changes could bring the U.S. system closer to the approval process used by many other countries. Instead of undermining confidence, a modernized U.S. regulatory system could actually increase the confidence of other nations in the safety of GE food.

MEANS OF ACHIEVING CHANGE

Beyond the disagreement over whether change is necessary at all, there are also issues associated with how change, if desirable, should be accomplished. Changes can be made by agencies, using their rulemaking and interpretative powers, and by Congress, which has sole authority to change the scope of an agency's inherent power. Clearly, some changes, particularly relating to procedures, are directly within the agencies' power to make through guidance and rulemaking.[19] Greater coordination among the agencies could also contribute to more efficient and less inconsistent regulation. But some argue that some of the needed changes can be made only through legislation.

The following are the arguments against pursuing changes via legislation.

The legislative route is undesirable, because agencies have sufficient legal flexibility to make any needed changes, and the risks of going to Congress to modify the law are too high. Major statutes like the FDCA, the PPA, and FIFRA are rarely amended, in part because historically the regulatory agencies have been able to find ways to interpret and

19 While relatively simple in concept, agency rulemaking is not necessarily easy or fast. For example, the EPA first proposed a rule to regulate pesticidal substances in genetically engineered plants in 1994, eight years after the Coordinated Framework was published. The final rules did not go into effect until 2001.

stretch their authorities to accommodate and regulate new products. In addition, attempting to change such laws can open a Pandora's box of controversial demands by a wide variety of constituencies. Congress cannot afford to devote significant attention to such issues every year because of the time and difficulty that it takes to reach agreement on controversial issues. Moreover, amendments can easily be adopted during the legislative process that may be unacceptable or unwelcome to some constituencies. It is very difficult, if not impossible, to control the outcome of a legislative process, given its vagaries and pressures. As a result, trying to modernize the agricultural biotechnology regulatory system by going to Congress for statutory changes risks changing the system in ways that are unpredictable and potentially undesirable. Furthermore, changing the law would subsequently require the agencies to implement the new provisions, opening the possibility for another round of uncertainties. The entire process would also take a good deal of time, during which there may be questions about products continuing to move through a regulatory system that will soon be changed.

A legislative change could also be interpreted incorrectly, particularly in skittish markets abroad. Changing a law may signal a more serious shortcoming in the regulatory system than a change in an agency regulation, which has more of the appearance of a "technical" fix. Some could view new laws as an admission that the current system is inadequate and that the products currently on the market have not been adequately reviewed for food or environmental safety.

The following are the arguments for using legislation to change the regulatory system.

Legislative change is needed because the laws themselves contain underlying flaws that are beyond the power of agencies to address in regulations. Further administrative patches to the system will only contribute to further confusion and threaten public confidence in the system. Legislative changes are needed to give agencies the explicit authority and tools they presently lack. With respect to concerns about undesirable legislative outcomes, those outcomes depend in part on whether or not the changes are hotly contested or broadly supported across a diversity of interested communities. Changes that have support among a broad set of key political constituencies could move relatively quickly. Some of the same concerns about uncertainty and the length of time legislation takes apply equally to the administrative rulemaking process. If the rationale presented for such changes is the need to modernize the system to anticipate future GE products, it is less likely that legislative change could be interpreted as an admission that current products may be unsafe. Ultimately, the risk to society of not fully addressing gaps and weaknesses in the current system outweighs the risk of pursuing the administrative and legislative solutions needed to modernize the Coordinated Framework.

Regulating Genetically Engineered Plants for Environmental Protection

Two federal agencies are responsible for assessing and managing environmental risks concerning genetically engineered (GE) plants: the Animal and Plant Health Inspection Service (APHIS) of the U.S. Department of Agriculture (USDA), and the Environmental Protection Agency (EPA). To date, more than 50 GE products have been reviewed by these agencies and received sanction for commercial use.[1] These products have been limited in scope; most are crops that have been rendered either insect resistant (through the insertion of *Bacillus thuringiensis (Bt)* genes, which have pesticidal properties) or herbicide tolerant. Their use has become widespread in the United States.[2]

The regulatory and scientific environment in which APHIS and the EPA operate is dynamic and has been rapidly evolving. In a recent report, the National Research Council (NRC) of the National Academy of Sciences stated:

The committee finds that APHIS and other regulatory agencies charged with assessing the safety of transgenic plants face a daunting task. This is so in part because environmental risk assessment of transgenic plants is new and in part because the social context in which regulatory decisions about transgenic organisms must now be made is dramatically different from the one in which these agencies have been accustomed to working (NRC 2002b).

This chapter describes and analyzes a variety of issues relating to the regulatory system governing GE crops and environmental protection. It contains four main sections. The first provides a summary of the key issues in play. The second describes in detail the existing regulatory system involved in managing the environmental impacts of GE plants and microorganisms. The third section delves further into the key issues and concerns regarding the existing system. And the fourth and final section offers several possible means for addressing those issues and concerns, if policy makers determine that changes are needed.

Overview of Key Issues

One of the major concerns regarding GE plants has been their potential to negatively affect the natural environment. Particular concerns have been raised, for example, about the potential for such plants to escape cultivation, persist in the environment, and become weeds. GE plants could also cross-pollinate with wild or weedy relatives, creating new, more adaptable and aggressive weeds. Weeds can, of course, given the right circumstances, displace natural flora and fauna and degrade ecosystems. In some cases, cross-pollination

1 For a list of GE plant-incorporated protectants currently registered with the EPA, see http://www.epa.gov/pesticides/biopesticides/pips/pip_list.htm. For the current status at APHIS of petitions regarding the deregulation of GE plants, see http://www.aphis.usda.gov/bbep/bp/petday.html. For a list of biotechnology consultations completed by the Food and Drug Administration, see http://www.cfsan.fda.gov/~lrd/biocon.html#list.

2 In 2002, GE varieties accounted for 81% of the soybeans, 73% of the cotton, and 40% of the corn grown in the United States (NASS 2002; for global figures, see James 2002).

can also negatively affect biodiversity and reduce genetic diversity in plant populations (NRC 2002b). GE crops that have been modified to produce their own pesticides or to contain pharmaceutical or industrial substances could have unintended adverse impacts on the organisms and wildlife that feed on those crops (NRC 2000 and 2002b).[3] (The potential of GE crops modified to produce pharmaceutical or industrial substances to become mixed with food crops is a related issue that is discussed in the next chapter.) Scientists have also raised concerns that increasing insects' exposure to *Bt* toxins through the extensive planting of *Bt* crops could accelerate the rate at which the pests become resistant to those toxins (EPA FIFRA SAP 2002).[4]

GE plants also have environmental benefits, which regulatory agencies are required to consider. For example, the use of such crops can reduce the use of chemical pesticides that can have adverse environmental impacts (Carpenter 2001; EPA 2001a). Also, GE herbicide-resistant crops are well suited to no-till agriculture, which can reduce soil erosion (CTIC 2002).

APHIS's regulations for GE plants were written under the authority of the Federal Plant Pest Act (FPPA; formerly 7 USC § 150aa et seq.), a law that was designed primarily to protect commercial agriculture from plant pests. To use this authority, the agency's regulations classify most GE plants as "plant pests" or potential "plant pests." At the field trial stage, technology developers are required to either (depending on the plant) notify APHIS if they are going to plant a new type of GE crop, or apply for and receive a permit from the agency to do so. To commercialize a GE plant, a technology developer may request that APHIS "deregulate" that plant, which amounts to a finding by APHIS that the plant is not in fact a plant pest. Once deregulated, the plant can be grown without APHIS oversight (7 CFR Part 340).

Questions have been raised as to whether APHIS's plant pest approach provides the necessary coverage and authority to adequately oversee the diversity of GE products that are, or soon will be, under field trial or possibly commercialized in the United States. Some GE plants may not be covered by APHIS's current regulations. Some GE plants could be grown for commercial purposes without an affirmative finding of safety by APHIS and without an opportunity for prior public notice or public comment. Concerns have also been raised about the adequacy of APHIS's authority to address intrastate releases of GE plants, environmental risks that are not also plant pest risks, and post-market problems that may arise. The NRC concluded a review of APHIS's regulation of GE plants in 2002; Figure 2.1 contains a summary of its findings. Potential new authorities under the Plant Protection Act (PPA; 7 USC § 7701 et seq.), which passed in 2000 and subsumed the old FPPA, may provide an approach for addressing the perceived weaknesses in the plant pest approach. APHIS has yet to issue regulations concerning GE plants under the PPA. Targeted legislative changes to the PPA are also an option.

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3 In 2000, a scientific paper created worldwide controversy when it found that Monarch butterfly larvae were killed by exposure to *Bt* pollen in a laboratory setting. Subsequent studies found that the risk to the larvae in the field was likely to be quite low for most approved varieties of *Bt* corn, but the incident focused attention on the issue of impacts on nontarget organisms (PIFB 2002).

4 In addition to environmental concerns, unintended gene flow from genetically engineered crops can have financial implications for non-GE-crop growers. The adventitious presence of GE traits in crops intended to be marketed as non-GE or organic, or the presence of GE traits that have not been approved for import into some countries, can damage the economic value of those crops. These important marketing issues are not addressed in this report, however, as it is focused on the regulatory system for food safety and environmental protection.

Figure 2.1 Summary of the National Research Council Report

Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation

In 2002, the National Research Council's Committee on Environmental Impacts Associated with Commercialization of Transgenic Plants issued its final report. The report reviewed the scientific basis that supports the USDA's oversight of environmental issues related to transgenic plants and their products. It contained the following key findings and recommendations. (Page numbers are noted in parentheses.)

- "[T]he transgenic process presents no new categories of risk compared to conventional methods of crop improvement but…specific traits introduced by both approaches can pose unique risks" (5).
- "[I]t should be possible to relatively quickly screen modified plants for potential environmental risk and then conduct detailed tests on only the subset of plants for which preliminary screening indicates potential risk" (5).
- "…APHIS and other regulatory agencies charged with assessing the safety of transgenic plants face a daunting task…. [T]he APHIS regulatory system has improved substantially since it was initiated" (8).
- "…APHIS currently has the authority to base regulatory scrutiny on potential plant pest status, regardless of the process of derivation, and therefore can theoretically regulate any transgenic plant. However, the only practical trigger used by APHIS is the presence of a previously identified plant pest or genes from a plant pest in the transformed plant. Other operational triggers are needed for transgenic plants that may have associated risks but lack the above characteristics" (8).
- "[T]he notification process is conceptually appropriate, but there is a need to reexamine which transgenic plants should be tested and commercialized through the notification process" (9).
- "[T]he APHIS [deregulation] process should be made significantly more transparent and rigorous by enhanced scientific peer review, solicitation of public input, and development of determination documents with more explicit presentation of data, methods, analyses, and interpretations" (10).
- "[T]here is a need for APHIS to actively involve more groups of interested and affected parties in the risk analysis process while maintaining a scientific basis for decisions" (12).
- "The committee specifically noted understaffing in the area of ecology" (12).
- "The committee recommends that the regulations to enforce the [Plant Protection Act] be developed in a manner that will increase the flexibility, transparency, and rigor of APHIS's environmental assessment process" (16).

The EPA regulates pesticidal substances produced by certain GE plants—called "plant-incorporated protectants" (PIPs)—under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA; 7 USC § 135 et seq.). Many aspects of PIP regulation are uncontroversial. However, recent studies have raised questions about the adequacy of farmers' compliance with insect-resistance management refugia requirements for *Bt* corn and cotton. Due to the unique nature of PIPs, farmers have no legal responsibility to the EPA to comply with such requirements, an issue that has raised concerns about the adequacy of the EPA's enforcement authority (Jaffe 2003a and 2003b; Weise 2003). Concerns have also been raised about the fact that developers may test some PIPs on experimental plots without notifying the EPA, which raises the possibility of unapproved GE substances making their way into the environment and the food supply. If a change in this exemption is desirable, the EPA should be able to undertake it administratively, without the need for legislative change.

The EPA also regulates certain GE microorganisms—and may regulate GE "plant-made industrial products" (PMIPs)—under the Toxic Substances Control Act (TSCA; 15 USC § 2601 et seq.) There is a lack of clarity about the EPA's regulation of PMIPs, in addition to debate about the scope of the agency's legal authority under TSCA to regulate GE products. The agency could develop regulations for plants that produce PMIPs, which would clarify some of the ambiguity over the regulation of these products.

The Existing Regulatory System

Under the current system, APHIS claims broad jurisdiction over all GE plants. The EPA regulates pesticidal substances produced in some GE plants, and it may also have a role in the regulation of plant-made industrial products. The Food and Drug Administration (FDA) may also have some authority over plants that contain drugs and biologics; its regulatory system is reviewed in Chapter 3.

APHIS

This section discusses APHIS's general statutory authority to regulate plant pests and noxious weeds and then reviews how APHIS has applied those laws to date to regulate GE plants.

The Regulation of Plant Pests and Noxious Weeds Under the Plant Protection Act

The Plant Protection Act (7 USC § 7701 et seq.) was enacted in June 2000 and was a consolidation and expansion of several older laws relating to the regulation of plant pests and diseases, including the FPPA (formerly 7 USC § 150aa et seq.), the Plant Quarantine Act (formerly 7 USC § 151 et seq.), and the Federal Noxious Weed Act (FNWA; formerly 7 USC § 2801 et seq.). The PPA repealed these old laws, but included a savings clause that provided that regulations promulgated under them would remain in effect until APHIS issued new regulations under the PPA (7 USC § 7758(c)). No new regulations have yet been promulgated.

Under the new Plant Protection Act, APHIS is responsible for preventing the importation and interstate dissemination of plant pests and noxious weeds.[5] The PPA authorizes

5 Technically, the PPA gives authority to the Secretary of Agriculture. The Secretary has the authority to delegate this responsibility to APHIS. For the purposes of this report, APHIS is described as having the legal authority.

APHIS to regulate "any plant, plant product, biological control organism, noxious weed, article, or means of conveyance" that could spread a plant pest or noxious weed (§ 7712). The definition of "plant pest" in the PPA is very broad, and includes living organisms that could injure, damage, or cause disease in any plant or plant product.[6] The definition of "noxious weed" in the PPA is also quite broad; it includes "any plant or plant product that can directly or indirectly injure or cause damage to crops (including nursery stock or plant products), livestock, poultry, or other interests of agriculture, irrigation, navigation, the natural resources of the United States, the public health, or the environment" (§ 7702(10)).

Under the PPA and its predecessor laws, APHIS exercises and enforces its authority through regulations, quarantines, and remedial measures. APHIS has three basic types of authority: general, emergency, and extraordinary emergency. Under its general authority, APHIS is authorized to require permits, certificates of inspection, treatments, and systems approaches to prevent the spread of plant pests and diseases. APHIS can also require that plants be grown or handled under post-entry (i.e., post-import) conditions for the purpose of determining whether they are plant pests or noxious weeds. APHIS has broad authority to conduct warrantless inspections for plants, plant pests, noxious weeds, and other articles subject to the PPA. APHIS can take action against any plant, including any plant progeny, plant product, article, or means of conveyance that has moved into the United States, or interstate, that there is "reason to believe" was infested or infected by or contained any plant pest or noxious weed (§ 7714).[7] APHIS has the ability to levy civil penalties or to seek criminal penalties for knowing violations.[8]

If an owner of an infected plant, plant pest, or noxious weed is ordered to take action to treat or destroy the article and does not do so, APHIS can take the action and recover the cost from the owner (§ 7714(b)). APHIS's general authority also includes the ability to quarantine a state or part of a state to prevent the interstate movement of a plant pest or noxious weed.[9] APHIS can cooperate with states, farmers' organizations, and/or individuals to eliminate the spread of plant pests and noxious weeds (§ 7751).

By declaring an emergency, APHIS can transfer funds from any agency or corporation of the USDA for the purpose of controlling or eradicating a plant pest or noxious weed

6 Specifically, the PPA defines a 'plant pest' as "any living stage of any of the following that can directly or indirectly injure, cause damage to, or cause disease in any plant or plant product: (A) a protozoan. (B) a nonhuman animal. (C) a parasitic plant. (D) a bacterium. (E) a fungus. (F) a virus or viroid. (G) an infectious agent or pathogen. (H) any article similar to or allied with any of the articles specified in the preceding subparagraph" (§ 7702(14)).

7 APHIS can "hold, seize, quarantine, treat, apply other remedial measures to, destroy, or otherwise dispose of, any plant, plant pest, noxious weed, biological control organism, plant product, article, or means of conveyance" moving into or through the United States or interstate (§ 7714(a)).

8 Civil penalties are authorized up to $50,000 for an individual and up to $250,000 for any other person, or twice the gross gain derived by the violator, or twice the gross loss caused to any other person. Knowing violations are subject to criminal penalties in accordance with Title 18 of the U.S. Code and up to one year of imprisonment or both (§ 7734(b).

9 It has typically been the agency's policy to always quarantine an entire state (not part of a state), unless that state is able to prevent intrastate movements from a smaller quarantined area. That is because APHIS does not have the power to enforce a quarantine within a state unless it either declares an extraordinary emergency or there is 'interstate movement' of the plant pest or noxious weed. The quarantine laws require movement across a state line, unlike laws that can regulate intrastate activities that "substantially affect" interstate "commerce" (see, e.g., Wickard v. Filburn, 317 U.S. 111 (1942)).

(§ 7772). Typically, when an emergency is declared, the USDA will seek to transfer funds from the Commodity Credit Corporation.[10]

APHIS can also declare an extraordinary emergency to respond to intrastate movements and activities regarding plant pests and noxious weeds, if a state is unable or unwilling to take appropriate measures. Before APHIS can declare an extraordinary emergency, it must consult with the Governor or other appropriate state official and publish the decision and the reasons for it in the *Federal Register* (§ 7715(b)).[11] When APHIS takes actions under an extraordinary emergency, it is authorized (but not required) to pay compensation for economic losses incurred. If the agency decides to pay compensation, its determination as to the amount paid is final and is not subject to judicial review, except to ensure that it is not an arbitrary or capricious decision (§ 7716(e)). There is no requirement that just compensation or fair market value be paid.

Traditionally, therefore, states are responsible for taking initial remedial action concerning plant pests and noxious weeds within their borders; APHIS is responsible for taking action to control or prevent the interstate movement of plant pests and noxious weeds. In the absence of interstate movement, APHIS can take remedial measures only after declaring an extraordinary emergency, which requires the agency to find that a state is unwilling or unable to take adequate actions and that there is an actual threat to plants or plant products from a new plant pest or noxious weed.

APHIS's Policies for Regulating GE Plants

In 1987, APHIS exercised its authority under the FPPA, the Plant Quarantine Act, and the Agricultural Marketing Act of 1946 and issued regulations that presumptively classified most genetically engineered plants as plant pests or potential plant pests. Under the regulations, which govern the "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," the introduction of such organisms and products is prohibited unless APHIS is notified of the introduction, or APHIS issues a permit authorizing the introduction, or the introduction is conditionally exempt from the necessity of such notification or permit (7 CFR Part 340).[12]

These regulations, which were "grandfathered in" in 2000 under the Plant Protection Act (7 USC § 7758(c)), are based almost solely on APHIS's authority to regulate plant pests under the old FPPA. As discussed later in this chapter, the newer Plant Protection Act may provide APHIS with broader authority to address GE plants than the FPPA. However, APHIS has not yet issued new regulations under the PPA, and the regulations issued in 1987

10 The Commodity Credit Corporation is an agency within the USDA that was created during the Great Depression to stabilize farm income and prices.

11 To declare an extraordinary emergency, APHIS must also find that a plant pest or noxious weed exists in and threatens plants or plant products of the United States. It must also find that the affected state is unable or unwilling to take adequate measures to prevent the dissemination of the plant pest or noxious weed (§ 7714).

12 The exemptions are for *E. coli* genotype K-12 (strain K-12 and its derivatives), sterile strains of *Saccharomyces cerevisiae,* and asporogenic strains of *Bacillus subtilis* under certain conditions regarding shipping containers and the way the organisms are maintained to prevent the dissemination of plant pests. These bacteria are exempted because they are used as noncoding promoters and do not make specific proteins within plants, nor are they reproduced within plants. Certain *Arabidopsis* material is also exempt (7 CFR § 340.2(b)).

remain in effect. The discussion in this section therefore addresses APHIS's policies and practices under 7 CFR Part 340 and the FPPA.[13]

Under Section 340.1 of the regulations, GE plants and plant products are considered to be plant pests if the donor organism, recipient organism, vector, or vector agent used in their creation is a member of a genus (listed in the regulations) known to contain plant pests.[14] A plant or plant product is subject to regulation if it (1) meets the definition of a plant pest, or (2) is an unclassified organism, and/or (3) is an organism whose classification is unknown. Further, a plant or plant product is subject to regulation if (1) it contains such an organism, or (2) it contains any other organism or product altered or produced through genetic engineering that APHIS determines is a plant pest or has "reason to believe" is a plant pest. Excluded from regulation are recipient organisms that are not plant pests and that have resulted from the addition of genetic material from a donor organism where the material is well characterized and contains only noncoding regulatory regions (§ 340.1).

The remainder of this section covers four aspects of APHIS's policies regarding GE plants: regulatory steps; the application of the National Environmental Policy Act (NEPA); data requirements and risk assessment; and transparency and public participation.

Regulatory Steps

APHIS's regulations control the importation, transportation, and planting of covered GE plants. A party desiring to import, transport interstate, or plant (i.e., "environmental release") a GE plant must either (1) notify APHIS that an introduction will be made (§ 340.3) or (2) apply for a permit (§ 340.4).

Notification is a streamlined procedure that is intended to allow the introduction of a low-risk potential plant pest material without a permit under circumstances that ensure the plant's containment and destruction. Notification is not a formal review and permitting process. Rather, it requires that the material meet specific eligibility criteria[15] and that certain performance standards be met to ensure containment.[16] Notification is available for plant

13 APHIS's Part 340 regulations were amended in 1993 to allow for the notification process (APHIS 1993) and further amended regarding notification and deregulation in 1997 (APHIS 1997).

14 See http://www.invasivespecies.org/Qualstatement.pdf for APHIS's official list of genera containing known plant pests.

15 The eligibility criteria for notification cover characteristics of the regulated articles that are relevant to their risk profile as plant pests. The criteria require that:
- the plant species be a species that 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)).

16 These performance standards have been established via rulemaking. The general standards govern how plants in the notification track should be shipped, stored, planted, and field tested to ensure that regulated articles do not escape from containment nor persist in the environment (7 CFR § 340.3(c)).

species that are not listed by APHIS as noxious weeds (at 7 CFR Part 360)[17] and are not considered weeds in the area of the proposed release. The standards state general requirements but leave applicants the flexibility to meet them according to their own circumstances (NRC 2002b, 109). Nearly 99% of all field tests, importations, and interstate movements of GE plants are performed under the notification process (CEQ and OSTP 2001).

When APHIS receives a notification application, regulatory staff review it for qualification and completeness. If the paperwork meets muster with APHIS staff, it is then sent on to state regulators for their review. The notification review process must be completed within 30 days for field trials and within 10 days for the interstate movement of a regulated article. APHIS's acknowledgement of a notification applies 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)).

Permits are required for the importation, interstate movement, or planting ("environmental release") of GE plants that are covered by the PPA and are not eligible for the notification process. A permit must be obtained for each plant/field trial combination; the permits generally last for a year and are renewable. Applicants may also request nonrenewable, 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 (§ 340.4). All genes to be tested in that crop (including uncharacterized genomic project genes not eligible under notification) can be included.

APHIS requires that permit applications be submitted at least 120 days prior to the intended field test of a GE plant. APHIS has 30 days to conduct a review to ensure that adequate data has been supplied by the permit applicant. If adequate data has not been submitted, the clock stops ticking on APHIS's 120-day deadline.[18] A permit may impose limitations on transportation or planting to prevent the escape of plant material that may pose a pest risk to the environment. The permit holder must allow APHIS and appropriate state inspectors access to the field trials and must notify APHIS of any unusual occurrences. After concluding a field trial, the permit holder must submit field test reports within six months (§ 340.3(d)(4)).

APHIS forwards the applications for all permits—usually with confidential business information redacted—to state regulators in the states where release is planned or importation is destined. This is done to notify states of the requested action and to allow states to review and comment on proposed releases or importations/movements. However, it is unclear whether states have authority to block permits. APHIS has said that states "must concur with APHIS" before any action can take place, but APHIS makes the final determination of whether to issue a permit based on all available information (CEQ and OSTP 2001, 29).[19]

17 See http://www.aphis.usda.gov/ppq/permits/fnwsbycat-e.PDF for the federal noxious weed list.

18 Data provided for a permit application must ensure that (a) the GE plant is adequately characterized; (b) no transgenic material will persist in the environment; (c) unintentional effects, if any, can be restricted to the confined field site and receiving facility; and (d) for field testing, the plants are managed such that there is no environmental risk after the field trial is completed (NRC 2002b, 110-111).

19 In addition to reviewing the data submitted by the technology developer, APHIS may also consider whether the state is able to help monitor permit compliance if the permit is granted.

"Nonregulated status" may be available for a developer who wishes to engage in widespread planting (or marketing of seeds) of a covered GE plant (§ 340.6). For APHIS to grant a nonregulated status petition, the studies and data submitted in support of the petition, including the results of field trials conducted under a permit or notification, must demonstrate that there will in fact be no significant plant pest risk from widespread planting (APHIS 1996). Petitioning APHIS for a determination of nonregulated status is the typical route to commercialization of a GE plant, since it allows planting with less restrictive conditions than those often imposed by a permit or the notification process.[20] A GE crop that has been approved for nonregulated status is said to be "deregulated."

Application of the National Environmental Policy Act

The National Environmental Policy Act applies to "major federal actions significantly affecting the quality of the human environment" (42 USC § 4332(2)(c)). To comply with NEPA, federal agencies, in taking actions such as issuing permits, must first determine through an environmental assessment (EA) whether the proposed action would have a significant impact on the environment. If an agency finds that an action would have no significant impact, it issues a finding of that fact—referred to as a "finding of no significant impact" or FONSI. However, if the agency cannot make such a finding, it is required by NEPA to issue a "detailed statement" (called an "environmental impact statement," or EIS) on, among other things, the environmental impact of the proposed action and the alternative actions considered (§ 4332(2)(c)). Public comment is required on a draft EIS before it is made final. The Council on Environmental Quality (CEQ) has issued regulations specifying how agencies should comply with NEPA (40 CFR §§ 1500-1508). CEQ regulations provide that certain types of federal activities may be categorically excluded from NEPA review (§ 1508.4).[21]

Like all federal agencies, then, APHIS is subject to NEPA. APHIS has issued a broad categorical exclusion for notifications and confined field trials (7 CFR § 372.5(c)(ii)), although the agency may require an EA or an EIS for a field release if it has the potential to have a significant environmental impact, as in a case where it involves "new species or organisms" or "novel modifications that raise new issues" (§ 372.5 (d)(4)). APHIS requires an EA for deregulation petitions (CEQ and OSTP 2001). When APHIS publishes an EA, it provides for a public comment period of at least 30 days and then publishes its finding of no significant impact in the *Federal Register*. To date, APHIS has not conducted an EIS for any deregulation petition.

Data Requirements and Risk Assessment

In considering whether to acknowledge a notification, grant a permit, or grant a nonregulated status petition, APHIS requires the notifier or applicant to submit data regarding a number of potential risks. Such risks include whether the GE plant might (1) expose other

20 Once a GE plant is deregulated, subsequent progeny of the plant are also deemed deregulated. The NRC has raised particular concerns that stacked genes developed through the cross-breeding of two or more GE plants with different GE traits may pose new risks and should not necessarily be considered deregulated by APHIS (2002b, 233-235).

21 Most of the EPA's decision making under its environmental laws has been deemed to be functionally equivalent to the NEPA process, and as a consequence the EPA is not required to comply with the procedural requirements of NEPA.

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 (nontarget 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 (APHIS 1996).

The scope of the data required depends on the type of permission sought by the applicant. Under both a notification and a permit, parties must submit field test reports within six months, including methods of observation, resulting data, and analysis regarding all deleterious effects on plants, nontarget organisms, and the environment (7 CFR § 340.4(f)(9)). Appendix B contains a complete list of the types of data APHIS requires for notifications, permits, and nonregulated status petitions.

Transparency and Public Participation

APHIS lists on its web site, shortly after it is received, summary information of notifications and permits for interstate movement, importation, and field testing. The status of these items and some additional information is available through an online database (CEQ and OSTP 2001).[22] Technically, the public can comment on the permits and notifications. However, there is no designated public comment period, and the public typically does not know if the agency has already made a decision, as it does not post such decisions online right away. APHIS may or may not use the public input in its decision making, and the agency does not provide an explanation for decisions made on notifications or permits. An NRC report noted that APHIS's risk assessments for notifications and field trials are not subjected to external scientific review or any other public input (2002b). As noted previously, environmental assessments are not prepared for notifications or field trials, since the assumption is that confinement conditions will preclude any significant environmental effects (7 CFR § 372.5(c)(3)(ii)). Recently, in an effort to enhance transparency in its regulatory enforcement actions, and, presumably, to create a disincentive for noncompliance with permit restrictions, APHIS announced that it will make all permit violations publicly available (2003d).

Petitions for nonregulated status provide for greater transparency and public participation. Upon receipt of a completed petition for nonregulated status, APHIS publishes a notice in the *Federal Register* soliciting public comment for 60 days. On request, the public can receive a free copy of the petition. Subsequently, when a draft environmental assessment is completed, APHIS publishes in the *Federal Register* a notice of its availability and solicits public comments on it for at least 30 days. Copies of the draft EA are available electronically. Following consideration of comments and a decision to deregulate a plant, APHIS publishes its determination that the plant does not meet the definition of a regulated article and its FONSI under NEPA.[23] APHIS's analysis and other related decision documents are placed on the agency's web site.

22 The database can be found at http://www.aphis.usda.gov/bbep/bp/status.html

23 If APHIS cannot make a favorable decision, the agency can either reject the petition, or the petitioner has the option to withdraw the petition and submit it later, presumably with additional data to support it.

In any kind of application to APHIS regarding GE plants, an applicant can claim confidentiality for financial or commercial information that the applicant does not want disclosed for competitive reasons. Under the Freedom of Information Act (FOIA; 5 USC § 552 et seq.), agency records that contain "trade secrets and commercial or financial information obtained from a person and privileged or confidential" are exempt from public disclosure. Further, 18 USC § 1905 makes it a criminal offense for a federal official to disclose "confidential business information" (CBI).

To claim confidentiality for data, applicants must submit a written justification to support each claim. Trade secrets (i.e., information relating to production processes, such as formulas, processes, quality-control tests and data, and research methodology) may be claimed as CBI. This information must be (1) commercially valuable, (2) used in the applicant's business, and (3) maintained in secrecy (APHIS 1985). According to the NRC (2000, 172), in 1999, in response to state regulators' concerns that permit applicants were designating most submitted information as CBI, APHIS provided clarification on the kinds of submissions that should not be designated as confidential.

On occasion, APHIS has used public workshops and conferences to receive public guidance and comment on scientific or public policy concerns related to a specific GE plant or a class of GE plants.[24] However, the NRC has encouraged APHIS to more aggressively use outside scientific review to ensure the adequacy and rigor of its review process and to encourage general public input into the process of policy development with regard to GE plants (2002b, 168-175).

APHIS's Experience with GE Plants

Using the regulatory system just described, APHIS has been responsible for the largest number of regulatory actions to date among the three principal agencies overseeing agricultural biotechnology (APHIS, EPA, and FDA). APHIS's online database lists 8,758 notifications and 1,180 environmental release permits granted since the beginning of the agency's biotechnology program.[25] Developers have initiated the deregulation process for 93 crops—though that number includes some initial petitions that were withdrawn and later resubmitted. To date, 61 petitions have been approved.[26]

APHIS recently reported that "of the 7,402...field tests [of GE plants that] APHIS regulated from 1990 to 2001, 115 resulted in compliance infractions. This means that overall compliance rates with APHIS's biotechnology regulations exceeded 98 percent; or that less than 2 percent of all GE field tests resulted in compliance infractions" (APHIS 2003a).

As mentioned at the outset of this chapter, the NRC, in reviewing APHIS's regulatory process, underscored the "daunting task" for regulatory agencies charged with assessing the safety of GE plants. While critical of the rigor and procedures used in some past regulatory decisions, the NRC noted that the "APHIS regulatory system has improved substantially since it was initiated." The NRC also noted that while "the learning process at APHIS has

24 See http://www.aphis.usda.gov/brs/index.html#documents for a list of public workshop reports and summaries.

25 The database can be accessed at http://www.nbiap.vt.edu/cfdocs/fieldtests1.cfm

26 See http://www.aphis.usda.gov/bbep/bp/petday.html for the list of deregulated plants.

not come without missteps, the agency seems to use them as opportunities for further improvement" (2002b).

The EPA

The Environmental Protection Agency is involved in regulating the human and environmental safety of certain GE plants, plant products, microorganisms, and microbial pesticides through its implementation of two laws: the Federal Insecticide, Fungicide, and Rodenticide Act (7 USC § 135 et seq.) and the Toxic Substances Control Act (15 USC § 2601 et seq.).

FIFRA's history dates back to the early 20th century, when legal protections for farmers against ineffective or misbranded pesticides were a driving concern. Over the years, FIFRA has been amended by Congress in a manner that has shifted its focus from a truth-in-marketing law to one that serves to protect human health and the environment from unacceptable risks related to the use of pesticides. In 1972, FIFRA was "modernized," and its implementation was shifted from the USDA to the newly created EPA. While recent amendments to pesticide laws have largely required that pesticide food safety risks be regulated primarily using risk-only assessments,[27] environmental safety reviews continue to occur under a risk-benefit balancing rubric. Under FIFRA's pesticide registration process, the EPA has broad authority to restrict or ban the manufacture and use of pesticides. FIFRA's enforcement authority, however, is largely delegated to state governments (7 USC § 136w-1).

TSCA was enacted by Congress to give the EPA the ability to obtain information on thousands of industrial chemicals produced in or imported into the United States, and to regulate certain chemicals where appropriate. Using TSCA's mandatory pre-manufacture notification authority, the EPA screens new chemicals and can require testing, exposure controls, and hazard communication for those chemicals that may present an unreasonable risk to human health or the environment. TSCA is a federally managed law, and its enforcement is not delegated to states (ChemAlliance 2001).

In the early 1990s, the EPA's Office of Pollution Prevention and Toxic Substances began organizing a new program within the EPA to regulate GE microorganisms and certain GE plants. This undertaking culminated in 1997 with new TSCA regulations, to ensure the safety of GE microorganisms (40 CFR Parts 700, 720, 721, 723 and 725). Regarding FIFRA, the EPA published regulations in 1994 requiring notifications of experimental releases of GE microbial pesticides (40 CFR § 172.43). And in 2001, the agency finalized new FIFRA and Food, Drug, and Cosmetic Act (FDCA) regulations, to ensure the safety of plant-incorporated protectants (40 CFR Parts 152 and 174).

This section describes FIFRA and TSCA authorities and regulations in more detail, both in general and as the laws apply, or do not apply, to GE plants and plant products. FIFRA is discussed first, then TSCA.

The Regulation of Pesticides Under FIFRA

The EPA regulates pesticides under the authority of FIFRA. FIFRA provides, with few exceptions, that no person may distribute or sell in the United States any pesticide that is

27 See e.g., the Food Quality Protection Act of 1996, PL 104-170.

not "registered" (7 USC § 136a(a)).[28] The EPA regulates pesticides under FIFRA to determine their environmental safety. In addition, under the authority of the FDCA, the EPA establishes levels at which each pesticide's presence in food is safe for consumption (i.e., they set "tolerances"), or they determine that a pesticide is of such a low food safety risk that it does not require a tolerance and therefore is granted a "tolerance exemption" (21 USC § 346a). Before the 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 USC § 136a(c)(5)). FIFRA defines "environment" as "water, air, land, and all plants and man and other animals living therein, and the interrelationships which exist among these" (§ 136(j)). "Unreasonable adverse effects on the environment" is further 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" (§ 136(bb)).

The EPA's evaluation of a pesticide proposed for registration includes an assessment of data from tests done by the producer of the pesticide according to EPA guidelines, and an evaluation of whether the pesticide has the potential to cause adverse effects on humans, wildlife, fish, and plants, including endangered species and nontarget organisms.[29] (Figure 2.2 contains an outline of the EPA's pesticide registration process.) Prior to full-scale commercial use, pesticides are regulated by the agency through "experimental use permits" (EUPs; § 136(c)). EUPs are often used by pesticide developers to collect data in support of pesticide registration applications. Under current EPA regulations, developers conducting small-scale, experimental field trials of pesticides (not exceeding a cumulative total of 10 acres) are not required to obtain EUPs or notify the EPA before field trials, as long as certain conditions are met (40 CFR § 172.3(c)(1)). One of those conditions is that any food or feed crops affected by the test must be destroyed or fed to animals involved in experimentation, unless the pesticide has a pesticide residue tolerance or an exemption from a tolerance (§ 172.3(c)(1)(ii)).

Under the FDCA, 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 USC § 342). The FDCA states that a pesticide chemical residue in or on food is not safe unless it meets a tolerance level (i.e., maximum allowable level) that the EPA has established for that pesticide, or unless the EPA has exempted the pesticide from the requirement of a tolerance for the residue (§ 346a(a)(1)).

28 '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" (§ 136(u)). FIFRA allows the 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 (§ 136w(b)(2)). To qualify for an exemption, a pesticide must pose a low probability of risk to the environment (including humans and other animals, plants, water, air, and land) and cause no "unreasonable adverse effects" to the environment even in the absence of regulatory oversight (40 CFR § 152.25).

29 Because the EPA's laws provide the functional equivalent of NEPA, the agency is largely exempt from the procedural requirements of that law (*Environmental Defense Fund v. EPA*, 489 F.2d 1247, 1256-57 (D.C. Cir. 1973); CEQ and OSTP 2001).

Figure 2.2 The EPA's Pesticide Registration Process

(From 40 CFR Part 152)

I. Manufacturer submits pesticide registration application. The application includes:

Required test data:

- Product chemistry
- Human and environmental assessment for food safety
- Tolerance information, consisting of information about pesticide residues on food
- Proof that the manufacturing process is reliable

Labeling information:

- Occupational data
- Directions for use
- Appropriate warnings

II. The EPA processes applications and conducts evaluation. Upon arrival:

1. The EPA assigns applications to the appropriate pesticide division, where they are processed and tracked. For each application, a project manager is then assigned to:
   - Complete a detailed review of the application
   - Assign and coordinate the appropriate scientific review
   - Set priorities and a timetable
   - Coordinate administrative action
   - Communicate with the applicant, otherwise known as the registrant, about the review

   A. The EPA evaluates human health risks (emphasizing sensitive groups such as children and immune-suppressed individuals) by reviewing data on:
      - Aggregate risks—through food, water, and residential uses
      - Cumulative risks—from different pesticides with the same effects

   B. The EPA evaluates occupational risks

   C. The EPA evaluates environmental risks by reviewing data on:
      - Potential for groundwater contamination
      - Risks to endangered species
      - Potential for endocrine-disruption effects

2. Risk assessment and peer review:
   - The EPA compiles all the scientific data on the pesticide product into a comprehensive health and environmental risk assessment to determine the impact that the product or ingredient will have on the human population and surrounding environment
   - The health and environmental risk assessment undergoes a process of peer review by scientific experts

3. Risk management and regulatory decisions, where the EPA:
   - Considers its risk assessments and the peer review
   - Reviews risk mitigation measures
   - Researches alternative pesticides already registered
   - Coordinates risk management with applicants

Section 408(b) of the FDCA authorizes the EPA to exempt a pesticide from the requirement of a tolerance if it meets the food safety standard 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" (§ 346a(c)(2)(A)). In determining whether a pesticide chemical residue is safe, the 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" (§ 346a(b)(2)(D)(vi)).

Under FIFRA, the EPA has extensive legal authority over the registrants and users of pesticides to enforce the terms of a pesticide registration. The EPA can cancel a registration and stop the sale of a product if its registrant violates the terms and conditions of the registration. The use of a pesticide by any person in violation of the conditions and restrictions on the label is a violation of federal law (7 USC § 136j(a)(2)(G)). To investigate and correct violations of registration or label conditions, the EPA can:

- require that registrants and applicators of restricted (more risky) pesticides keep detailed records (§ 136i-1);
- inspect establishments where pesticides are made, stored, or sold and be given access to records kept there (§ 136g); and
- enter premises where restricted pesticides are used (§ 136g).

If a pesticide proves to be an "imminent hazard," the EPA can unilaterally and immediately remove it from the market (§ 136d).

The EPA is able to require and enforce a wide range of use conditions and restrictions on a pesticide, including production caps and planting restrictions. In general, all pesticide use restrictions are implemented and enforced via a label affixed to the pesticide container. The EPA also has authority to quickly modify the use restrictions on an existing label to address an emerging risk concern (§ 136d).

The EPA can impose civil penalties up to $5,500 per violation for registrants or commercial applicators and up to $1,100 for private applicators (such as farmers) after a warning for a first offense.[30] The EPA also can seek criminal penalties for knowing violations, with fines and prison up to $55,000 and one year for registrants and commercial applicators and $1,100 and 30 days for private applicators (§ 136l(b)). The EPA can also require registrants to report adverse effects and to generate and submit data on newly identified safety or environmental issues (§ 136d).

FIFRA gives the states primary enforcement authority (§ 136w-1). So, states typically enact their own pesticide laws that are generally consistent with FIFRA. Because FIFRA does not authorize entry onto farms to monitor compliance with labeled use restrictions on pesti-

30 Under FIFRA, this warning letter is the only enforcement tool available against each new violation by a farmer, regardless of the severity of the violation and the ramifications of that particular violation (Aidala, pers. comm.).

cides, such access to monitor compliance with refuge requirements or animal feed restrictions is a matter of state law (Taylor and Tick 2003).

Although the EPA finalized a rule specifically for PIPs (40 CFR Parts 152 and 174), it has not issued new data requirements. Guidance on data requirements thus dates from the prior 1994 guidance (EPA 1994). The EPA's data requirements for the registration of a PIP are included in Appendix B.

The pesticide registration process includes opportunities for public input. Applications for a pesticide registration are subject to public notice and comment. For a review under FIFRA, the EPA publishes in the *Federal Register,* "upon receipt," a completed pesticide data application and must provide at least 30 days for public comment (7 USC § 136a). The establishment of a pesticide tolerance or exemption under the FDCA is also subject to notice and comment. Once the EPA determines that a tolerance petition is complete, the agency must provide public notice of its findings establishing the tolerance or tolerance exemption, which is done through a "notice of filing" in the *Federal Register*. Public comments can be made at that time, but the agency is not required to respond them. The agency can then issue a final tolerance-setting regulation without further notice or public comment. Within 60 days of the issuance of a final regulation establishing a pesticide tolerance, any person may file an objection to the decision and request a public evidentiary hearing concerning the tolerance. Then, only after stating the EPA's action(s) regarding each objection raised during the evidentiary hearing, the agency can issue a final regulation.[31] Finally, if the agency wishes to modify, suspend, or revoke an existing tolerance or tolerance exemption, it must provide a 60-day public comment period before doing so (21 USC § 346a(e)(2)).

While not required to do so, the EPA can and does meet with groups and individuals to discuss proposed regulatory actions. The EPA makes available for inspection and copying the studies submitted, with CBI information excluded; such materials are available via requests under FOIA (5 USC § 552 et seq.).

Section 10b of FIFRA requires the protection of trade secrets and CBI (7 USC § 136h). However, Section 10b(d)(1) limits confidentiality protection for safety and efficacy data (unless disclosure of such data in turn would disclose manufacturing or quality-control processes, the method for detecting any deliberately added inert ingredient, or the identity or percentage quality of any deliberately added inert ingredient) (§ 136h(d)(1)). Even information in these excepted categories can be disclosed if the EPA determines that disclosure is "necessary to protect against an unreasonable risk of injury to health or the environment" (§ 136h). FIFRA also provides for the disclosure of certain nonconfidential data 30 days after registration (§ 136a(c)(2)(A)).

The EPA's Policies Regarding GE Plant-Incorporated Protectants

In the early 1990s, the EPA initiated an extensive science and policy review process to implement its regulatory responsibilities under the Coordinated Framework. In 1994, the agency published a proposed rule that asserted that plants that had been genetically engineered to

31 Unlike the FDCA, FIFRA has restrictions on judicial challenges to agency determinations and provides no right for citizen suits (7 USC § 136n).

produce pesticidal substances would be considered pesticides under FIFRA and would therefore require approved pesticide registrations before they could be grown commercially. The regulated articles were called "plant-pesticides" in the proposed rule (EPA 1994).

For a variety of reasons, this proposed rule was viewed as controversial by many, with scientific societies and academic researchers being particularly critical (IFT 1996). Nevertheless, the EPA and technology developers operated under the framework of the rule for a number of years. In 2000, the NRC conducted an extensive study of the EPA's approach to regulating plant-pesticides. In general it endorsed the EPA's approach, but it also made several recommendations for modification (2000; see Figure 2.3). In part reflecting the NRC's recommendations, the EPA published its final rule in July 2001. In the final rule, the EPA changed its regulatory focus from "plant-pesticide" to "plant-incorporated protectant," which it defined 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."[32] The definition also included: "contains any inert ingredient contained in the plant, or produce thereof" (40 CFR § 174.30).

Under the final rule, the 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 (§ 174.25). These exempt PIPs are still subject to the EPA's adverse-event reporting requirements (§ 174.71).

The EPA's rule enables the agency to impose extensive use restrictions and post-approval monitoring requirements on PIP-containing plants and to require PIP registrants to report any adverse effects possibly associated with their products (§ 174.71) As with conventional pesticides, the EPA has the authority under FIFRA to suspend or cancel the use of a pesticide if it later poses unacceptable environmental or human health risks (7 USC § 136d(b)). The rule also maintains the existing exemption for experimental use permits for small-scale field tests under 10 acres.[33]

Of course, GE plants with PIPs are not conventional pesticides, so their regulation is somewhat unique. Usually, the EPA ensures the safe use of a pesticide through pesticide labeling. Distributors and users are required to comply with restrictions on labels; uses that violate a label are unlawful and are enforceable by the EPA. In the case of PIPs, however, the regulated pesticidal substance is produced in the tissues of the growing plant and is not present in the seed itself—the actual commodity that is distributed and sold. There are therefore no labels on bags of GE seed that contain EPA-enforceable use restrictions. While registrants and seed companies have direct legal obligations to the EPA as a result of the

32 'Genetic material necessary for the production' means both genetic material that encodes a substance or leads to the production of a substance, and regulatory sequences. It does not include noncoding, nonexpressed nucleotide sequences (40 CFR § 174.3). If the EPA did not include genetic material in the definition of a PIP, then the genetic material would be considered simply part of the whole plant and consequently exempt, since living plants are exempt from FIFRA (§ 152.20). Under the final rule, the EPA regulates the pesticidal substance expressed by the plant, not the plant itself (§ 152.20(a)(4)).

33 Given the possibility that even small-scale releases of microbial organisms could spread in the environment, the EPA has issued separate rules requiring notification and prior approval for small-scale experimental testing of GE microbial pesticides (40 CFR § 172.45). These requirements parallel the requirements for notification and approval of nonpesticidal GE microbes under TSCA, discussed later in this section.

Figure 2.3 Summary of the National Research Council Report

Genetically Modified Pest-Protected Plants: Science and Regulation

In 2000, the National Research Council's Committee on Genetically Modified Pest-Protected Plants released its final report. The purpose of the committee's work was to "investigate risks and benefits of genetically modified pest-protected plants, and the Coordinated Framework... affecting the use of these plants" (2). The report outlined a variety of potential health and ecological risks from pest-protected plants, and identified a number of areas in which future research is needed. It also discussed the positive and negative elements of the regulatory framework that existed at that time and suggested improvements for the review and exchange of scientific information. The following were among the report's recommendations. (Page numbers are noted in parentheses.)

- "[B]oth conventional and transgenic pest-protected crops could have effects on nontarget species, but these potential effects are generally expected to be smaller than the effects of broad-spectrum synthetic insecticides" (9).
- "[P]ollen dispersal can lead to gene flow among cultivated crops and from cultivated crops to wild relatives but...only trace amounts of pollen are typically dispersed further than a few hundred feet" (9).
- "[P]est resistance to pest-protected plants could have a number of potential environmental and health impacts such as a return to the use of more harmful chemicals or replacement of an existing pest-protected variety with novel varieties for which there is less information available about health and environmental impacts" (10).
- "Given that transfer and manipulation of genes between sexually compatible plants could potentially result in adverse effects in some cases (for example, modulation of a pathway that increases the concentration of a toxicant), and given the public controversy regarding transgenic products, EPA should reconsider its categorical exemption of transgenic, pest-protectants derived from sexually compatible plants" (13).
- "The quantity, quality and public accessibility of information on the regulation of transgenic pest-protected plant products should be expanded" (15).
- "The USDA should clarify the scope of its coverage as there are some transgenic pest-protected plants that do not automatically meet its current definition of a plant pest" (16).
- "To improve coordination among the three regulatory agencies, EPA, FDA, and USDA should develop a memorandum of understanding for transgenic pest-protected plants that provides guidance to identify the regulatory issues that are the purview of each agency...and establishes a process to ensure appropriate and timely exchange of information between agencies" (16).
- "A solid regulatory system and scientific base are important for acceptance and safe adoption of agricultural biotechnology, as well as for protecting the environment and public health. In general, the current U.S. coordinated framework has been operating effectively for over a decade. However, the committee has identified several kinds of improvements that would be helpful in the face of a larger number of commercialized transgenic pest-protected plants and novel gene products introduced into these plants. Those improvements might be necessary for increased confidence in U.S. agricultural biotechnology both domestically and worldwide" (18).

registration,[34] farmers have no legal responsibility to the agency to comply with use or planting restrictions in the absence of a label setting out those restrictions (Taylor and Tick 2003).[35] To deal with this unique issue, the EPA requires registrants, as a condition of registration, to develop compliance assurance programs, through which they require farmers to agree, as a condition of sale, that they will comply with planting restrictions.[36] Thus, the EPA must rely on registrants and seed distributors to monitor and enforce farmers' compliance with safety requirements (e.g., insect-resistance management refugia, geographically designated planting prohibitions). Under the compliance assurance programs, registrants must refuse to sell *Bt* seed to any farmer who is shown to be a serious repeat offender.

Although the EPA finalized a rule specifically for PIPs (40 CFR Parts 152 and 174), it has not issued new data requirements. Guidance on data requirements thus dates from the prior 1994 guidance (EPA 1994). The EPA's data requirements for the registration of a PIP are included in Appendix B.

In addition to the opportunities for notice and public comment associated with registrations and pesticide residue tolerances generally, the EPA has regularly used independent science advisory panels to provide guidance on key scientific issues regarding the use and regulation of PIPs, as well as to peer review the scientific rigor of regulatory assessments for PIPs (see e.g., EPA FIFRA SAP 2002).[37]

The EPA's PIPs rule requires upfront substantiation any time a CBI claim is made, and it strongly encourages registrants to limit the amount of data claimed as CBI (40 CFR § 174.9) Appendix B contains a listing of the data that applicants must submit in order to make a case for a CBI claim.

The EPA's Experience with PIPs

Most of the PIPs approved by the EPA contain the *Bt* toxin to promote insect resistance in crops. In 1995, the EPA registered the first Bt plant-incorporated protectants for use in the United States. Since then, the agency has registered 16 *Bt* PIPs, although only 10 of these registrations are currently active (EPA 2002).[38] All Bt PIPs on the market today have been granted tolerance exemptions for food and feed uses under Section 408 of the FDCA.[39]

34 At the EUP stage, the EPA also requires cooperators—private and public researchers who conduct field trials of experimental PIPs—to abide by FIFRA label restrictions for PIPs.

35 If the seeds themselves were considered pesticides, a field of *Bt* corn potentially could be regulated as a "pesticide-producing establishment," with each *Bt* corn plant effectively being regulated as a pesticide manufacturing facility. Such a legal construct, if enforced per existing regulations for pesticide manufacturing facilities, would make each *Bt* corn farmer liable for specific registration, reporting, recordkeeping, and inspection requirements (in addition to other regulations) that would be onerous if applied to any farming operation.

36 An example of literature produced by one developer to be used with farmers can be found at http://www.monsanto.com/monsanto/us_ag/content/biotech_traits/rr_bollgard_cotton/2004_bollgard.pdf

37 See http://www.epa.gov/pesticides/biopesticides/pips/index.htm for reports and summaries of public meetings and science advisory panel meetings.

38 See http://www.epa.gov/pesticides/biopesticides/pips/pip_list.htm for a list of the PIPs currently registered with the EPA.

39 Tolerance exemptions have also been granted for the inert ingredient residues and genetic material that are associated with herbicide-tolerant crops, which are regulated by APHIS.

Between 1994 and 2001, the EPA declared several other non-*Bt* PIPs to be exempt from tolerance requirements under the FDCA—specifically, those that incorporate viral coat proteins (VCPs) to induce resistance to disease-causing plant viruses.[40] These VCP products were determined to be exempt from FIFRA registration requirements, but the EPA nonetheless reviewed them for food safety and granted them exemptions from tolerances under the FDCA.[41]

By virtue of its primacy in the regulation of *Bt* products, the EPA has had to address some of the most volatile controversies regarding GE plants. Issues concerning the possible impact of *Bt* toxin dispersed by the pollen of GE crops and its impact on nontarget insects, in particular the monarch butterfly, largely fell to the EPA to address (PIFB 2002). Also, the potential for the overuse of *Bt* crops, resulting in the rapid development of insect pests' resistance to *Bt* and thus the loss of the pesticide's long-term utility to farmers, continues to be addressed by the EPA. In recent years, the EPA has taken steps to address nontarget species and insect-resistance concerns during the course of the re-registration process for *Bt* corn and cotton varieties (EPA 2002).

Finally, the agency's decision to grant a split registration—allowing the feed use, but not the food use, of StarLink corn (because of unresolved concerns about potential allergenicity)—contributed to a significant food recall effort. The recall occurred after Aventis, the product developer, failed to comply with its license agreement to ensure that all StarLink corn was segregated from the food marketing chain. As a result of the recall, Aventis and the food industry lost hundreds of millions of dollars (Lueck 2000), and critics of the regulatory process were quick to point out that the violation was not discovered by food safety regulators, but by an environmental advocacy group monitoring the food supply (Gillis 2004; Pollock 2000). Subsequent to this crisis, Aventis withdrew its product from the market, and the EPA announced it would no longer grant split registrations for GE crops (EPA 2002).

The Regulation of Chemicals Under TSCA

A second law, the Toxic Substances Control Act, provides the EPA with additional authority to regulate some types of GE organisms, possibly including plants and plant products. In this section, the EPA's regulation of chemical substances under TSCA is reviewed, followed by a discussion of the law's potential application to some GE plants. Unlike with FIFRA, the EPA has not yet indicated whether or how TSCA might apply to GE plants or plant products.

TSCA provides the EPA with the authority to regulate chemical substances that may present an "unreasonable risk to human health or the environment" during manufacture, processing, distribution in commerce, use, or disposal (15 USC § 2605). TSCA provides the EPA with authority over "chemical substances," which are defined as "any organic or inorganic substance of a particular molecular identity" except for drugs, cosmetics, food and food additives, pesticides, medical devices, firearms, and tobacco (§ 2602(2)(A)). TSCA does not explicitly define unreasonable risk, but the EPA does list factors that it will need to consider when assessing the safety of a chemical. (See Appendix B.) Under TSCA, the EPA

40 The EPA decided in 2001 to no longer generally exempt viral coat proteins from FIFRA and FDCA regulation (as recommended by the NRC in its 2000 report).

41 APHIS reviewed the environmental safety of these VCP products under its FPPA authorities.

is required to consider both the extent to which risks would be avoided by regulation and the burden imposed by that regulation (§§ 2605(c)(1) and 2604(b)(4)(A)(ii)).

A major objective of TSCA is to characterize and evaluate the risks posed by a chemical to humans and the environment before the chemical is introduced into commerce. TSCA thus may require that manufacturers perform various kinds of health and environmental testing, use quality control in their production processes, and notify the EPA of information they gain on possible adverse health effects from the use of their products. Under TSCA, "manufacturing" is defined to include "importing," and thus all requirements applicable to manufacturers apply to importers as well (ChemAlliance 2001).

Section 5 of TSCA (15 USC § 2604) requires all companies that intend to manufacture or import a new commercial chemical substance to submit a "pre-manufacturing notice" (PMN) to the agency at least 90 days prior to the manufacture or import of the substance.[42] The PMN notice is required to include information and test data in the possession or control of the notifier that could assist the EPA in evaluating the new chemical substance's potential adverse effects on human health and the environment. If the EPA takes no regulatory action on a manufacturer's PMN within 90 days, the company can legally begin to manufacture or import the new chemical substance (§ 2604(c)). However, this deadline can be extended by the voluntary assent of the manufacturer or through suspension requests by the EPA. The agency can require additional data or testing only after determining that the substance may present an unreasonable risk or will have substantial exposures. If the EPA determines that there is a reasonable basis to conclude that the substance presents an unreasonable risk, the agency is required to take action to prevent the risk before the product can be manufactured or imported (§ 2604(f)).

To control unreasonable risks that may be presented by a new chemical substance, the EPA may enter into a Section 5(e) "consent order" that lays out the specific conditions and precautions that are necessary to ensure that the use of the new chemical does not pose an unreasonable risk. The consent order's restrictions are binding only on the manufacturer submitting the PMN. For that reason, the EPA also usually issues a "significant new use rule" (SNUR) after it issues a consent order; a SNUR is intended to bind other chemical companies to the same restrictions placed in the consent order. A SNUR effectively requires a manufacturer to notify the EPA at least 90 days before undertaking "a significant new use" of a chemical listed on TSCA's Inventory of Chemical Substances (§ 2604(a)(1)(B)).

TSCA provides a blanket exemption from the PMN process for research and development uses of a chemical (§ 2604(h)(3)). If a person exercises this exemption, he or she must abide by specific recordkeeping, production volume, and other requirements set out in 40 CFR § 720.36 and § 720.78.

Section 6 of TSCA (15 USC § 2605) gives the EPA authority to regulate *existing* chemical substances that could present unreasonable human health or environmental risks. Among other things, the EPA can:

42 Section 5's pre-manufacturing notification requirements apply to chemicals introduced after 1979 or otherwise not on the EPA's TSCA Inventory of Chemical Substances (§ 2602(9). In the case of GE microorganisms, discussed in the next section, the EPA has taken the position that all new genetically engineered microorganisms are "new chemicals" for the purposes of the law (EPA 1997).

- prohibit or limit the amount of a substance that is produced or distributed in commerce;
- prohibit or regulate the manner or method of commercial use;
- require warning labels and/or instructions on containers or products;
- require recordkeeping by producers; and
- specify disposal methods.

The EPA also may impose any of these requirements in combination or for a specific geographical region. However, TSCA requires the EPA to use the "least burdensome" regulatory approach in regulations under Section 6, even in controlling unreasonable risks (§ 2605(a); CRS 1999). This requirement, as interpreted by court decisions, has limited the agency's use of such controls. (See *Corrosion Proof Fittings v. EPA* (1991, CA5) 947 F2d 1201.)

Under TSCA, the EPA can collect information from chemical manufacturers (§ 2607). TSCA requires manufacturers to retain records of adverse events and report any new information that a chemical substance presents a "substantial risk of injury to health or the environment" (§ 2607(e)). TSCA provides for penalties of up to $27,500 per day per violation (§ 2615). The law also allows for emergency actions to respond to imminent hazards (§ 2606).

Regarding public participation, the EPA, upon receipt of a PMN, seeks public comment prior to making a final decision on the safety assessment and regulation of a new chemical. Typically, the EPA will announce several new PMNs or new actions on existing PMNs in one *Federal Register* notice, with the listing covering TSCA activity over a period of a few days to one month. The notice lists each EPA case number, receipt date, projected notice end date, manufacturer of the chemical, use of the chemical, and the chemical itself, in table form. Often, the manufacturer's identity is listed as confidential, and the chemical and its use may be described generically so as not to reveal the specific chemical identity and use. The public is invited to call the EPA for additional information on specific PMNs; however, the agency also clearly states that information claimed as CBI by the manufacturer is not part of the public docket for a PMN (40 CFR § 720.95). Often, there can be a delay of several days to several weeks before a listing of active PMNs is published in the *Federal Register*.

Although TSCA allows for broad claims of CBI (15 USC § 2613), the EPA limits confidentiality claims for data supporting a PMN by requiring companies to substantiate any claims of confidentiality. The EPA clearly articulates the process by which manufacturers can assert claims of confidentiality (40 CFR §§ 720.80-720.95). Submitters who claim chemical identity and/or use as CBI must provide generic information for release to the public.

Under TSCA, citizens can petition the EPA to issue a rule regulating a specific chemical (15 USC § 2619). The EPA must grant or deny a petition within 90 days. The petitioner can seek judicial review of any petition denial (§ 2620).

The EPA's Policies for Regulating GE Products Under TSCA

In the 1986 Coordinated Framework, TSCA was seen as the "gap-filler"—the law that would cover any GE organisms not covered by other laws (OSTP 1986). The EPA has interpreted the definition of "chemical substance" in TSCA to cover intergeneric microorganisms (microorganisms created by the insertion of genes from another genus). In 1997, the EPA issued final

regulations under its TSCA authority for these GE microbial products (40 CFR Parts 700, 720, 721, 723, and 725). GE microorganisms subject to TSCA might be used for specialty chemical and enzyme production, bioremediation, biosensors of environmental contaminants, biofertilizers, ore mining, oil recovery, biomass conversion, or other uses (BIO 2003).

The EPA's TSCA regulations have established a notification specifically designed for GE microorganisms: the "microbial commercial activity notice" (MCAN). An MCAN must be submitted to the EPA at least 90 days before an intergeneric microorganism is used for commercial purposes, and the EPA has 90 days to review the submission. Some intergeneric microorganisms are exempt.[43] As with conventional chemicals, the EPA reviews the GE microorganisms for their potential to cause unreasonable risks to human health and the environment. During the review period, the agency may take action to prohibit or limit the production, processing, sale, use, and disposal of microorganisms that raise health or environmental concerns. If the 90 days pass without action by the EPA, an MCAN submitter is legally free to manufacture or import the GE microorganism without controls. As with conventional new chemicals, however, the review period can be extended by EPA for good cause (15 USC § 2604(c); 40 CFR § 725.56) or suspended altogether with the mutual consent of the EPA and the MCAN submitter (40 CFR § 725.54).

While most small-scale research and development of new chemicals is exempt from reporting requirements under TSCA, the EPA was concerned about the ability of even small quantities of biological material used in research to escape and reproduce. As a result, the agency's biotechnology regulations also address intergeneric microorganisms used in research and development for commercial purposes and create a vehicle for reporting on the testing of new microorganisms in the environment—the "TSCA experimental release application" (TERA) (40 CFR Part 725, Subpart E). A TERA must be submitted to the EPA at least 60 days prior to initiating field trials. TERAs are intended to be more flexible than MCANs, in order to meet the needs of researchers, and the review period for TERA applications is shortened to 60 days (§ 725.50(b)(1)).

With regard to public participation, all rulemakings concerning TSCA biotechnology are conducted with public notice and comment pursuant to the Administrative Procedures Act (5 USC § 552). Also, the EPA held public meetings and consulted with agency and government work groups when developing its current biotechnology regulations. In some cases, the agency consulted with its technical Federal Advisory Committee Act committees and science advisory boards on individual biotechnology product risks.

The EPA publishes a notice in the *Federal Register* announcing the receipt of each MCAN and exemption submission and provides a public comment period (40 CFR § 725.40). Unlike with PMNs, the EPA typically publishes MCAN notices on an individual basis. Each notice lists a tracking number, the microorganism and its use, as well as

43 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 are exempt from reporting when used in field tests because prior test experience indicates low environmental risk (40 CFR §§ 725.400-470). Other exemptions are noted at 40 CFR § 725.110 and subparts E and F (§§ 725.200-725.370).

the manufacturer or user of the microorganism. The notice also provides contact information, so that an interested party can request additional, non-CBI information. The public may also request, or the EPA may decide to convene, a public meeting of the EPA's Biotechnology Science Advisory Committee to review the safety of a particular GE microorganism (EPA 1993).

The EPA also provides public notification for all TERAs for GE microorganisms (40 CFR § 725.40). Because the TERA review period is only 60 days, opportunities for public comment may be moot. A TERA public notice lists the GE microorganism and the name of the submitter, a description of the microorganism and the purpose of its release into the environment, as well as the expected eventual use of the microorganism. The EPA also provides a summary of its risk assessment of the experimental release and the agency's conclusion, which may include guidance or restrictions that the EPA deems necessary to manage potential risks associated with the release. The agency also provides contact information for any individual who wishes to review the original nonconfidential TERA or the nonconfidential approval letter by the EPA.[44]

The EPA has consistently maintained that TSCA also provides the agency with authority to regulate GE plants containing industrial products, such as plastics, polymers, and oils (CEQ and OSTP 2001). However, these products were not mentioned in the Coordinated Framework, and the agency has not to date proposed any implementing regulations for them.

The EPA's Experience with GE Organisms

Between 1987 and 1997, the EPA reviewed 35 GE microbes; 19 submissions were for closed-system fermentation uses, 15 were for environmental introductions, and the nature of one submission was not characterized, presumably having been declared confidential by the submitter (EPA 1999). Since 1998, the agency has received nine MCANs, all of which were "dropped from review," and 12 TERAs, all of which were approved (EPA 2003).

Issues and Concerns Regarding the Existing System

This section describes issues and concerns relating to the existing regulatory system for GE plants and plant products as it relates to environmental protection. The section first discusses issues and concerns regarding APHIS's system, then the EPA's. For each agency, three general topics are discussed: overall responsibility and legal authority; pre-market authority; and post-market authority. Issues regarding clarity, transparency, and public participation at APHIS are also addressed.

APHIS

Overall Responsibility and Legal Authority

The regulatory approach adopted by APHIS raises a number of issues regarding responsibility and legal authority. First, it appears that a number of GE plants may not be

44 See http://www.epa.gov/opptintr/biotech/r010003.htm for an example of a TERA case summary.

covered by APHIS's existing regulations. As discussed previously, APHIS's system for regulating GE plants is based on its plant pest authority under the old Federal Plant Pest Act. The definition of a "regulated article" is based on the theory that any plant developed through genetic engineering that uses a donor, recipient, vector, or vector agent from a genus of plants known to contain a plant pest may itself be a plant pest (7 CFR § 340.1) While many GE plants will continue to be covered by these regulations because of the widespread use of DNA sequences from the cauliflower mosaic virus as promoters, some genetic engineering techniques do not involve the use of plant pests, including particle bombardment, the use of promoter sequences from non-plant pest sources, and electroporation.

Of course, the definition of "regulated article" also includes any GE plant that has been determined to be a plant pest or that APHIS has "reason to believe" is a plant pest, regardless of the use of plant pests or parts thereof in its creation (§ 340.1). This part of the definition in the law, however, is a functional one: APHIS needs a reasonable basis for believing that a GE plant could harm or injure plants or plant products. It is unclear how difficult it would be for APHIS to meet this standard. Given that APHIS has determined that many GE plants are not, in fact, plant pests and can be deregulated, at least some GE plants could fall outside the definition of "regulated article."

Second, APHIS's legal authority to address local and intrastate releases of GE plants is unclear. Under the former FPPA, APHIS has responsibility for controlling the interstate movement of plant pests, while states are responsible for intrastate matters unless APHIS declares an extraordinary emergency (Korwek and de la Cruz 1985). A declaration of extraordinary emergency requires, among other things, a finding that a state is unwilling or unable to take adequate measures to control a plant pest, as well as a finding that a plant pest is in fact a threat to plants or plant products. In its regulations based on the FPPA, however, APHIS covers any release of a GE plant into the environment, without regard to whether there is interstate movement or not.[45] But it is not clear that APHIS has the authority to take remedial action for purely intrastate activities without declaring an extraordinary emergency.[46]

Finally, APHIS's legal authority to consider environmental risks that are not plant pest risks appears to be constrained. The FPPA does not provide APHIS with authority over all environmental risks that might be posed by plants; APHIS's sole legal authority under the FPPA is to assess and manage plant pest risks—in other words, harm to plants. This responsibility arises from APHIS's historical mission of protecting commercially valuable crops from infestation and disease. GE plants however, raise environmental concerns that go beyond potential injury to plants. It is not clear that potential impacts on wildlife

45 APHIS's regulations define the term 'introduction' to include "release into the environment," which itself is defined as "the use of a regulated article outside the constraints of physical confinement..." (§ 340.1). As defined, the introduction of a regulated article includes purely local activity, such as the planting of a GE plant in a field. It might be argued that any release of a GE plant could presumed to be in interstate movement, given the potential for genetic material and pollen to flow after planting, but the same argument could be made for any non-engineered plant pest as well. Such an argument would undermine the traditional interstate movement/intrastate activity distinction made in the FPPA and retained in the PPA.

46 APHIS could levy civil penalties and seek criminal sanctions for violations of a permit even if such actions took place intrastate, but it could not directly order the destruction of the crop or take other remedial measures on an intrastate matter unless it declared an extraordinary emergency.

or nontarget organisms, for example, would be covered unless the case can be made that there is an indirect adverse effect on plants. In some cases, gene flow from GE plants could confer an advantage to a plant, but nevertheless contribute to a loss of biological diversity, which APHIS might legally not be able to consider. It is not even clear that weediness is an issue that falls under the definition of "plant pest," although APHIS routinely analyzes GE plants' potential for general weediness behavior as part of its permitting process.[47]

To some extent, NEPA supplements APHIS's authority under the FPPA and enables the agency to consider environmental risks beyond harm to plants. NEPA requires APHIS to assess all environmental risks in order to determine whether a proposed permitting or deregulating decision would constitute a significant impact on the environment. As a practical matter, APHIS can use this procedural requirement in NEPA to impose conditions on field trials to mitigate all environmental risks down to a point where the agency can issue a FONSI—a finding of no significant impact. Petitioners are unlikely to reject such conditions, since the alternative is preparing an EIS, which can be slow and expensive to produce. As a result, APHIS can and does use NEPA to indirectly address environmental risks that go beyond plant pest risks.

NEPA is primarily a procedural statute, however; it does not authorize APHIS to make decisions on the basis of environmental impacts that go beyond its statutory responsibility to protect plants. While NEPA instructs all federal agencies to take into consideration the environmental policies and goals set forth in the Act, it does not provide any additional substantive authority for an agency to act in those instances where an agency's underlying statutory authority is deficient. Thus, it is doubtful that NEPA provides the full range of legal authority APHIS may need to address all environmental risks (see *Zabel v. Tabb,* 430 F.2d 199, 209 (1970)). It is not clear, for example, that APHIS could, under its current regulations, legally deny a field trial permit or a petition for nonregulated status for a GE plant that could cause significant adverse environmental impacts, but is not a plant pest. A decision to grant a petition for nonregulated status is a finding by the agency that it does not have legal authority over the plant because the plant is not a plant pest within the meaning of the law. If a plant is not a plant pest, APHIS has no clear authority to deny a request for nonregulated status under its current regulations—regardless of the other potential environmental impacts the plant may have.[48]

47 APHIS might have been able to use its authority under the Federal Noxious Weed Act to address the potential of GE plants to become or to create noxious weeds, but the agency chose to base its regulations on the FPPA. However, even the FNWA, prior to the passage of the PPA, may not have provided sufficient authority, since the definition of 'noxious weed' in the FNWA included the concept that a noxious weed must be "new" or "not widely prevalent in the United States" (Korwek and de la Cruz 1985). It might have been difficult to sustain a finding that a new variety of a common food crop grown widely in the United States is covered by this definition.

48 APHIS typically prepares an EA for a petition for nonregulatory status, but even that may not be required. An argument could be made that a determination of whether or not an agency has jurisdiction over a product is not the type of agency action that requires an EA to be conducted. If a plant is not a plant pest, APHIS has no jurisdiction over it under its current regulations. Once a determination is made that a plant qualifies for nonregulated status, APHIS no longer has authority to take action regardless of any impacts an EA might demonstrate. On the other hand, such a determination is a mix of fact and law, including a consideration of the characteristics of the plant and its potential for environmental impacts, and as such it could be argued to the contrary that the decision is more discretionary than ministerial and that an EA should be required.

The significance of the uncertainties about APHIS's authority over some GE plants, intrastate activities, and non-plant pest environmental risks is open to debate. APHIS has asserted its authority over GE plants and environmental impacts, and to date there is no evidence to suggest that technology developers are challenging the notification, permitting, and deregulation requirements set out by the agency. On the other hand, APHIS's interpretations have not been challenged in court, leaving the enforceability of some of the agency's activities untested.

Pre-Market Authority

To the extent that a GE plant meets the definition of a plant pest under existing APHIS regulations, the agency has adequate authority under the FPPA to require the review and approval of the plant prior to its release into the environment. As noted above, APHIS has broad authority to require developers to submit data to demonstrate that a GE plant will not be a plant pest, and to approve field trials under conditions, imposed by a permit, to mitigate any plant pest concerns. If a developer violates a permit, APHIS has broad authority to take action to seize or destroy the crop (provided it has moved interstate or there is a declaration of extraordinary emergency) and to impose penalties. In an enforcement action to assess civil penalties, APHIS would not need to show that the GE plant actually harms or injures plants or plant products, but simply that the permit was violated.

However, current APHIS regulations do allow the commercialization of a GE crop without a prior affirmative approval by the agency and without public notice. Developers are not required to file a petition for nonregulated status before they produce a plant commercially. It is possible for developers to grow plants at a commercial scale under notification or field trial permits, even if the plants might pose some identifiable environmental or human health risk.[49] This situation raises several issues. Historically, the field trial permit and notification processes were intended to oversee research involving relatively few acres of plants that were potential plant pests. To the extent that GE crops are being grown commercially on larger acreage, they can have a greater environmental impact and also present more of a problem in managing unwanted gene drift to non-GE food crops. Since APHIS does not typically conduct an EA until the deregulation stage, in these situations APHIS would not have publicly assessed the environmental impacts of planting at a larger scale and made an affirmative decision that larger-scale production would have no significant impact on the environment.

Also, a petition for nonregulated status typically provides the only substantive opportunity for public notice and comment. Without such an opportunity before commercialization, limited public information is available about what is being grown commercially under permit.[50] Yet it is increasingly important for farmers, grain traders and processors, and food companies to know what is being grown commercially so that they can monitor

49 The NRC discussed this issue in detail in a recent report, using the example of Avidin corn as a case study (2002b, 180-181). Also, a low-nicotine GE tobacco has been grown for commercial purposes under a field trial permit, as the technology developer simultaneously pursued a nonregulated status petition with APHIS (Bundy, pers. communication).

50 While APHIS does post all field trial permits on its web site, the amount of information declared CBI varies and, if utilized broadly, can significantly limit the amount of product and field trial information that is available to the public.

their suppliers and ensure the identity of what they are buying and selling. This issue has become more of a concern given the field testing of GE plants that produce pharmaceuticals and industrial chemicals, and the increased market and regulatory scrutiny regarding the adventitious presence of unapproved GE traits in the marketplace. Recently, to at least partially address these concerns, APHIS added plant-made industrial products to the list of crops (already including "plant-made pharmaceuticals," or PMPs) that may not be grown under the notification process.[51]

Post-Market Authority

Typically, as a GE plant moves toward commercialization, the developer files a petition for nonregulated status. APHIS either grants the petition, finding that the GE plant is not a plant pest within the meaning of the law, or determines that plant pest risks may exist and thus allows the plant to be grown only under a permit that contains requirements to mitigate the potential risks.

For plants under permit, the primary post-market issue appears to be whether federal and state regulators have the resources necessary to oversee the increasing number of GE plants being grown under permits. APHIS has clear authority to require product developers, as part of a permit, to undertake risk mitigation and monitoring activities and to allow site inspections. The agency's recent guidance on PMPs and interim regulations on PMIPs are clear examples of how this authority can be exercised (APHIS 2003b and 2003c).

By contrast, APHIS would appear to have no continuing authority over crops that have been deregulated, since the legal effect of nonregulated status is that the agency lacks jurisdiction over the plant because it is not a plant pest. As a result, APHIS has no authority to require monitoring, perform site inspections, or require data reporting for an article that has been deregulated, a point that APHIS has acknowledged (CEQ and OSTP 2001). APHIS currently informs developers of deregulated plants that they have an obligation to report subsequent information that differs from what was submitted, but there is a serious question as to whether APHIS could enforce such a requirement.[52]

A deregulation decision does not preclude APHIS from subsequently re-regulating a plant, however, if additional evidence is obtained to show that it is indeed a plant pest or a noxious weed (under the PPA). Such re-regulation would require new scientific facts to show that the deregulation was an error, and that the plant is in fact a plant pest.[53] Until APHIS articulates a basis for re-regulating GE plants previously determined to not be plant pests, the authority and process for effectively asserting post-market controls on deregulated products will remain unclear.

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51 APHIS has not completely articulated its regulatory policies regarding PMPs and PMIPs. In 1993, APHIS precluded the testing of PMPs under notification (7 CFR § 340.3(b)(4)(iii)). On March 10, 2003, APHIS asked for comment on ways to improve specific aspects of its GE regulation program for the field testing of plant-based pharmaceutical and industrial compounds, including confinement measures, procedures to verify compliance, and ways to enhance transparency (2003c). On August 6, 2003, APHIS published in the *Federal Register* an interim rule that required introductions of industrial compounds to be done under permit and not under notification (2003b). This rule did not address whether or not PMIP and PMP compounds can be produced commercially under field trial permits. The next step for APHIS would most likely be the issuance of a proposed rule on these particular issues, if changes to the current policy are determined to be appropriate.

Another post-market concern, touched on previously, is that it is not always clear whether the federal government or a state has initial jurisdiction to take remedial measures with regard to a plant pest. States are responsible for intrastate matters, unless APHIS declares an extraordinary emergency (7 USC § 7715). APHIS may not be willing or able to declare such an emergency in some situations. For example, the agency may not have sufficient information to determine that a GE plant poses a plant pest risk or may hesitate to designate some plants, such as traditional crops, as plant pests in order to take action. In addition, the declaration of an extraordinary emergency allows APHIS to pay compensation for economic losses (§ 7715(e)), which can significantly increase the cost of a program—particularly if the compensation were paid in a crisis of StarLink magnitude.

Clarity, Transparency, and Public Participation

The NRC's 2002 report stated that "APHIS policies for public participation conform to a fairly narrow interpretation of those required by the federal Administrative Procedures Act." The NRC did note APHIS's use of the *Federal Register* to solicit public input on plant pest deregulation decisions, the issuance of permits (if an EA is conducted), and the alteration of the agency's internal regulatory procedures. The NRC also found that APHIS could and should, however, do more to obtain input from interested parties and, in particular, scientific experts, to support individual agency decisions and broader agency guidance. Of particular concern to the NRC were the ways GE plants could be grown and commercialized without public notice or external scientific review, most notably in the notification process (NRC 2002b, 168-170).

The NRC was also critical of the amount of information that is made available, noting that the "extent of CBI in company documents sent to APHIS hampers external review and transparency of the decision-making process" (2002b). A recent report from a public interest advocacy group noted an increasing tendency for information to be characterized as CBI.[54]

THE EPA

Overall Responsibility and Legal Authority

The EPA's authority to regulate pesticidal substances in GE plants, and its authority to establish tolerances and exemptions for tolerances for pesticide residues in food, appears to be

52 APHIS's letter granting a petition for nonregulated status states: "APHIS must be notified within five days in writing if any information comes to the applicant's attention that differs substantially from what was described in the petition and our environmental analysis." This adverse-event reporting statement was first inserted into a letter granting deregulated status to Dow's 100-136-01p HT and IR corn on June 28, 2001. However, there is nothing in the regulations requiring such adverse-event reports. It is difficult to see how APHIS could pursue criminal or civil penalties or legally take administrative action against an applicant for failing to provide such information on a plant that it has determined it has no basis to regulate. Arguably, however, APHIS could contend that the finding that a plant was not a plant pest was contingent on the developer agreeing to certain post-approval monitoring and reporting requirements.

53 It is arbitrary and capricious for an agency to reverse an earlier technical determination without an adequate and articulated basis. See *Motor Vehicles Mfrs. Ass'n v. State Farm Mut. Aut. Ins. Co.*, 463 U.S. 29 (1983).

54 "The percentage of field tests being conducted with introduced genes considered to be [CBI] has increased nearly every year from 0% in 1987 to 65.4% in 2000" (Caplan 2001).

clear. While there are several outstanding issues concerning exemptions,[55] the EPA has clear legal authority to apply FIFRA and the FDCA to GE plants that produce pesticidal substances.

By contrast, significant questions exist about the scope of the EPA's authority under TSCA to regulate GE plants and plant products. There is an initial legal question about whether the definition of "chemical substance" under TSCA (15 USC § 2601 et seq.) would reasonably include biological organisms like plants, trees, and animals. There is nothing in the legislative history of TSCA to suggest that Congress intended to give the EPA authority to regulate the environmental hazards of biological materials in addition to chemical ones; on the other hand, there is nothing to suggest that Congress intended to restrict the law's scope, either. The EPA's argument that TSCA applies to whole living organisms has drawn criticism (McGarity and Bayer 1983, 506), but to date the agency's application of TSCA to GE microorganisms has not been challenged.

In any event, the EPA's jurisdiction over plants under TSCA is limited by a number of exemptions in the law. For example, food, human and animal drugs, pesticides, and tobacco are all exempted from TSCA (15 USC § 2602(2)(B)). Whether the exemption for tobacco would also exempt any products (such as industrial chemicals) made from GE tobacco is a significant question, given the widespread use of tobacco as a production platform for modern biotechnology products.

In addition, TSCA is focused on commercial activities and provides only limited authority over research and development activities. In part, these restrictions are due to the assumption in the law that the research and development of chemicals poses little risk of exposure and therefore negligible hazard to the environment. However, even small quantities of viable biological material released to the environment have the potential to replicate or cause environmental harm. For that reason, the EPA's rules on GE microorganisms require a notification for experimental releases conducted "with the purpose of obtaining an immediate or eventual commercial advantage" for the manufacturer or distributor (40 CFR § 725.3). But it is not clear that TSCA would cover, for example, field trials of experimental PMIPs conducted by university researchers to understand basic plant mechanisms, or similar field trials prior to the commercial planting of a GE plant. Again, though questions may remain about TSCA's authority over plants, the EPA's regulations for GE microorganisms have not been challenged in court.

Finally, while TSCA would likely give the EPA authority over the industrial substances produced by GE plants to the extent they meet the definition of a new chemical substance or are covered by a significant new use rule, it is less clear whether the EPA has authority over the GE plant itself. The EPA may be required to consider a rule like that adopted for PIPs that exercises the agency's jurisdiction over the chemical produced by the plant rather than the plant itself.

55 In 1994, the EPA proposed a number of tolerance exemptions in its plant-pesticide rule (EPA 1994). Two of the exemptions were adopted in the final rules in 2001: (1) for PIPs developed through conventional breeding (40 CFR § 174.25) and (2) for the genetic material (i.e., DNA) that creates the pesticidal substance in the plant (§ 174.475). However, three proposed exemptions were not adopted in the EPA's final rule: (1) PIPs derived through genetic engineering from plants that are able to naturally propagate; (2) PIPs that act primarily by affecting the plant (such as causing the plant to have thicker wax cuticles); and (3) PIPs based on viral coat proteins (substances that encapsulate and protect the genetic material of certain plant viruses). The EPA invited public comment on these exemptions.

Pre-Market Authority

The EPA's regulations regarding PIPs provide adequate pre-market authority to ensure that PIPs are reviewed and approved for food safety and environmental risks before the crops are grown commercially. The EPA also requires experimental use permits for the planting of more than 10 acres of a GE crop, which enables the agency to impose conditions to prevent environmental risks.

One issue is whether the exemption for small-scale field tests (i.e., under 10 acres) is appropriate in the context of GE plants that produce pesticidal substances, given the possibility of gene drift to neighboring food crops. Currently, the EPA receives no notice and conducts no review of such small-scale plantings. However, EPA rules require that developers conducting small-scale, exempt field tests destroy any food or feed crops that may be affected by the PIP, if the PIP does not have a food residue tolerance or an exemption for a tolerance (40 CFR § 172.3(c)(1)(ii)). It is not clear, however, how the EPA monitors or ensures compliance with those provisions. Such exempt, small-scale tests would nevertheless be covered under APHIS's requirements either for a notification or a field trial permit.

To the extent that the EPA has authority over plants at all or over experimental field trials of PMIPs (discussed previously), a PMIP would be subject to the mandatory pre-manufacturing notification requirements of TSCA if it meets the definition of a "new chemical substance" covered by TSCA. However, the EPA's pre-market authority under TSCA differs from that of FIFRA. TSCA is a mandatory pre-manufacturing notification scheme for new chemical substances covered by the Act, but it is not a pre-market approval process. Unlike FIFRA, under TSCA the burden is not on the developer to show that a new chemical is safe, but instead is on the EPA to demonstrate that the chemical poses an unreasonable risk, based on an analysis of available data. Also unlike under FIFRA, the EPA has only limited power under TSCA to require testing to prove safety before a product goes to market. The agency only reviews new chemical substances for possible unreasonable health or environmental risks, and does not make affirmative approvals that products are safe. As a practical matter, a developer is unlikely to take a product to market if the EPA has expressed reservations about its environmental safety. As a legal matter, however, a developer may legally proceed to market unless the EPA acts to prevent it.

Post-Market Authority

Regarding FIFRA, farmers are not legally liable to the EPA, as noted previously, for violations of planting restrictions on PIP-containing plants. Instead, farmers are contractually liable to the PIP registrant or the seed seller. The EPA is therefore reliant on the registrants to enforce planting restrictions through contracts, education programs, and compliance monitoring. The current industry-sponsored, voluntary compliance scheme reportedly achieved in 2003 a national average of 92% farmer compliance with refugia planting requirements that are in place to manage European corn borer and Southwestern corn borer resistance to *Bt*, which is an improvement over the 87% compliance reported by the industry in 2000 (NCGA 2003b). However, some regional compliance estimates are well below the national average, with an estimated low of 62% compliance in the South during the 2002 growing season (Taylor and

Tick 2003).[56] A recent report by the National Agricultural Statistics Service, based on 2002 survey data, indicated that 20% of corn farmers in the corn belt failed to fully abide by *Bt* corn refugia planting requirements (Jaffe 2003a; NASS 2003).

Ongoing scientific and policy debates concerning the necessity, size, and structure of refugia to slow the development of insects immune to the *Bt* pesticide have been, and will continue to be, spirited. New varieties of rootworm-resistant *Bt* corn, one of which will be on the market in the 2004 growing season (Ritchie 2003), could significantly increase the number of acres planted with *Bt* crops in the near future and further intensify this debate. Some view the current levels of compliance as unacceptable and take the position that an industry-administered enforcement strategy will never adequately enforce *Bt*-producing seed planting restrictions, particularly if *Bt*-producing seed use expands in acreage and to new crops.[57] On the other hand, to date there is no evidence of any increase in *Bt* resistance in insect populations, so it could be argued that the program is working. In addition, the ability of federal and state regulators to solely administer and enforce regulations at the farm level is constrained by financial and staff resources (Taylor and Tick 2003).

For GE plants and plant products covered under TSCA, the EPA could impose requirements for post-market monitoring, inspection, and data collection under a Section 5(e) consent order if needed to prevent unreasonable risks. The EPA's consent order authority appears to provide the agency with ample authority to control or mitigate risks that were anticipated in a PMN review. TSCA's post-market authorities appear to be adequate, but the ability to use these authorities for any GE plants or, more specifically, PMIPs, hinge on the larger question of whether TSCA can and should be called upon to regulate these products.

Approaches to Resolving the Issues and Concerns

This section describes options for making the regulatory system governing GE plants more effective and clear and ensuring the protection of the environment and natural resources. Options for addressing APHIS's regulatory authority are discussed first; possible reforms to the EPA's system are second.

APHIS

Four topics are addressed below: options for addressing overall responsibility and legal authority concerns; options for strengthening pre- and post-market authority; options for improving transparency and public participation; and potential PPA-related legislative reforms.

Addressing Overall Responsibility and Legal Authority Issues

Two issues identified previously include APHIS's lack of clear legal authority to regulate some GE plants, and its lack of clear authority to consider environmental impacts other

56 As the European corn borer is also a pest in cotton, another crop that has extensive use of *Bt* varieties, this makes refugia compliance in the Southern corn- and cotton-growing regions all the more important. See, for example, http://msucares.com/pubs/techbulletins/tb224frames.htm

57 See, Jaffe 2003a and 2003b. "There's an inherent conflict of interest here," said Gregory Jaffe of the Center for Science in the Public Interest, which analyzed the NASS data. "The seed dealer sells to the [farmers]—he doesn't want to rat on them" (Weise 2003).

than harm to plants. As noted, some believe that APHIS's authority is adequate and that no change is needed, particularly given developers' compliance with APHIS's rules. If policy makers believe that APHIS's authority should be clarified, however, a number of policy options could be considered.

APHIS's current rules are based on the authority of the now-repealed Federal Plant Pest Act. The new Plant Protection Act, enacted in 2000, was intended to consolidate existing plant quarantine authorities into a single statute, and may also have provided APHIS with additional authority that it could use to address concerns with the existing regulatory scheme.[58]

In addition to covering plant pests and expanding their definition, the new PPA provides APHIS with much broader authority to regulate "any plant, plant product, plant pest, biological control organism, noxious weed, article, or means of conveyance" that could spread a plant pest or noxious weed (7 USC § 7712). And the PPA includes a new, broad definition of "noxious weed" as "any plant or plant product that can directly or indirectly injure or cause damage to crops (including nursery stock or plant products), livestock, poultry, or other interests of agriculture, irrigation, navigation, *the natural resources of the United States, the public health, or the environment"* (§ 7702; emphasis added).[59] This expanded definition appears to give APHIS clear jurisdiction over any plant that could damage the environment. APHIS would not be limited to regulating GE plants on the basis of their potential to harm plants, as it was under the FPPA. Therefore, the law appears to provide APHIS with a clearer, more specific grant of oversight authority under which the agency could, in theory, regulate if not *all* GE plants at least a broader array than under the current plant pest rubric.

In order to use the broader authority provided in the PPA, APHIS would need to issue new regulations that specifically cite the PPA's noxious weed provisions as well as its plant pest provisions. Such a revision would eliminate any confusion or ambiguity regarding APHIS's ability to regulate and take action regarding GE plants. The new regulations could explicitly convey APHIS's intention to use the authority of the PPA, including its noxious weed provisions, to fully consider the environmental impacts of GE plants as well as the economic interests of U.S. agriculture.

APHIS could also, in new regulations, define more clearly the environmental standard that it will apply in making regulatory decisions. APHIS has been using NEPA's procedural authority to assess environmental risks and to require mitigation to reduce impacts to a level of "no significant impact." To date, APHIS has concluded that all of its regulatory actions have met that standard. It is possible, however, that APHIS may at some point face a regulatory decision that will require an EIS. It is not clear what decision standard APHIS would use in a situation in which both significant benefits and significant environmental impacts exist. In new regulations, APHIS could propose a decision standard that—like the

58 As this report was going to press, APHIS published a programmatic environmental impact statement that, among other things, requested comment on using additional authorities under the PPA to regulate GE plants (APHIS 2004).

59 The PPA also eliminated the restriction in the older Federal Noxious Weed Act that a weed be "of foreign origin" and "new to or not widely prevalent in the United States." Also, the PPA grants new authority to APHIS to take action against noxious weeds, even if the plant in question is not listed on an official federal or state noxious weed list.

"no unreasonable risk" type of standard in FIFRA and TSCA—would give it the flexibility to weigh environmental risks and benefits as well as economic and other important policy goals.[60] In any event, APHIS could continue to use a single review process to meet both NEPA and PPA requirements. In addition, APHIS could articulate certain conditions or performance standards that, if met by a field trial sponsor, could result in a categorical exclusion from NEPA and therefore preclude the need for an EA or an EIS.

New regulations under the PPA that clarify jurisdictional authority and environmental standards could provide a sounder legal basis on which APHIS could take on the new applications of GE crops. Such regulations could also inspire greater confidence that the regulatory system is addressing the full range of possible environmental concerns.

Moving the regulation of GE plants to incorporate a noxious weed approach is not without drawbacks, however. While the authority exists to do so, it may be undesirable or unpalatable to APHIS to designate a variety of a widely-grown agricultural product as a noxious weed, for any reason. One possible response would be for APHIS to take the same approach as it does in its current GE regulations and refer to all covered GE plants as *regulated articles*.

An additional problem with using the noxious weed authorities of the PPA could arise in a StarLink-type situation. If APHIS designated a GE plant as a noxious weed and took remedial action under this authority, it opens the potential for the payment of compensation to farmers or other affected parties harmed by the noxious weed. In order to obtain all "contaminated" product, APHIS would probably have to declare more than one extraordinary emergency, as the contamination would likely occur in more than one state. When extraordinary emergencies are declared, APHIS risks having to pay for economic losses, regardless of fault. Since it may not be possible to collect all contaminated product without a broad offer of compensation, the potential costs to the government could be huge. These costs may create pressure not to exercise this authority, particularly if the harm is not to U.S. agriculture nor economic in nature, but is solely environmental. So, unlike the actual StarLink crisis, in which the product developer paid the cost of removing contaminated corn from the market, the use of noxious weed authorities by APHIS could open the government to paying such recovery costs.

Strengthening APHIS's Pre-Market and Post-Market Authority — A Tiered Permitting System

One issue identified previously is that some GE crops can be commercialized without a prior affirmative review by APHIS and without public notice. Also, APHIS may not have the legal authority to inspect or require monitoring of or data reporting on crops that have been deregulated. Questions also exist about how quickly and effectively APHIS can control an unanticipated risk related to a deregulated GE plant, particularly if that risk does not neatly jibe with the plant pest rubric of APHIS's existing regulations (NRC 2002b).

60 It is not clear how far APHIS may legally go in establishing an environmental decision standard solely through rulemaking. The term 'environment' appears only in the definitions of "move and related terms" and "noxious weed" in the PPA (7 USC § 7702), and not in a substantive provision. The PPA is silent as to how APHIS should take environmental impacts into consideration in making regulatory decisions. If such authority were desired, it would require an authorization from Congress.

One way to address these issues would be for APHIS to establish a more comprehensive and transparent approval process for GE plants in new regulations under the PPA. The regulations could set up a system in which all GE plants, or at least more than are clearly covered under the current plant pest paradigm, are required to be reviewed and authorized by the agency before they are tested in field trials or commercially produced. APHIS could issue permits for field trials of GE plants *and* for the general release of such plants (rather than deregulating them) after reviewing their potential environmental impacts.

Also, APHIS could require that no part of a plant given a permit for a field trial could be used commercially without a separate permit authorizing general release. The requirement for general release permits could apply to all GE plants sold in commerce, and would be intended to ensure that no GE plant is commercialized without affirmative agency approval. The requirement could subject crops that can now be commercialized without the filing of a deregulatory petition (e.g., crops that are still technically in the field trial stage) to a process that would require public notice.

A tiered permitting system for field trials could be established, through which all field trials would be permitted under one of three categories. The lowest-risk plants could be reviewed and approved under a simplified review category, which could be similar to the present notification process except that it would require an affirmative decision by APHIS. A standard review category could be for crops posing an intermediate level of risk and could be similar to the present field trial permit process. Field trials under both the simplified and standard review categories could be required to meet performance standards to prevent significant environmental impacts and could be categorically exempt from NEPA. A third category, enhanced review, could be available for crops that might pose novel issues, uncertainty, or higher levels of environmental risk. Field trials for crops in the enhanced review category could require an EA and a FONSI, or, if risks cannot be mitigated to the level of "no significant impacts," an EIS. In all cases, the public and the scientific community could have opportunities to comment on the criteria for categorization and the performance standards for simplified and standard review that would be intended to prevent significant environmental impacts.

This option could also include a general release permit for the commercial planting of a GE crop. The permit could be unrestricted or contain conditions or limitations as deemed necessary by APHIS. General release permits could require the preparation and publication of an EA and a FONSI, or alternatively, an EIS in those cases where the activity would pose a significant impact on the environment. General release permit holders could be required to report adverse events or conduct monitoring. See Figure 2.4 for a more detailed description of what a tiered permitting system could look like.

While a new tiered permitting system would provide greater transparency, certainty, and regulatory accountability, the concept has a number of downsides. Developing a new regulatory system could create a period of regulatory uncertainty that could slow product approvals while new rules are being developed. New affirmative approval requirements could, in some instances, lead to additional regulatory delay and increased costs for product approval, although such effects would depend at least in part on the kind of resources APHIS has to carry out the program.

Figure 2.4 A Tiered Permitting System for APHIS

The following is one way that APHIS could set up a tiered permitting system for GE plants. Field trial permits are discussed first, then general release permits.

Field Trial Permits

- All field trials would require a permit.
- Three **review categories** could be created for field trial permits—**simplified, standard, and enhanced**—so that the level of review and oversight for each field trial corresponds with the level of its anticipated risk to the environment. The developer could propose a category for each plant, but APHIS would make the final decision.
- The **criteria** used to assign a field trial to a given category could be developed with input from the scientific experts and public. APHIS could propose draft criteria, allow for public review and comment, and then issue final criteria. The criteria may need to be updated periodically, and public comment could be sought during each updating process. At a minimum, the following criteria could be considered in determining the category to which a field trial would be assigned:
  - **The nature of the host plant** – i.e., the potential for outcrossing and weediness and the prevalence of wild or weedy relatives in the vicinity of the proposed field trial.
  - **The nature of the genes/protein/trait implanted** – i.e., the previous history of those traits in other GE plants, the degree of characterization/specificity of the protein, and the toxicity/allergenic/bioactivity profile. This could also include whether the sequences that are present pose any risk of creating new plant viruses or whether they produce a pharmaceutical or other protein not intended for human consumption.
  - **The scale of the proposed trials** – i.e., the size of acreage of the proposed trials as well as the flora within the area in which the trials are proposed.
  - **The disposition of the nonviable harvested materials,** or raw agricultural commodities. This could be taken into consideration to preclude experimental crop residues from entering the food or feed supply.
- The **simplified review** category could be for the most benign plants. It could be comparable to the current notification process. Criteria for placement in this category could include the following:
  - The host plant is not listed on the APHIS noxious weed list.
  - The introduced genetic material is stably integrated.
  - The function of the introduced genetic material is known and its expression in the host plant does not result in plant disease.
  - The introduced genetic material does not encode for the production of an infectious entity, does not include products known or likely to be toxic to nontarget organisms, and does not include a pharmaceutical protein.
  - Plant viral proteins do not pose a risk of creating a new plant virus.
  - The plant does not contain sequences from human or animal viruses or sequences whose products are known or likely causal agents of disease in animals or humans.

Figure 2.4 A Tiered Permitting System for APHIS (...continued)

- Plants in this category could be handled as follows:
  - A thorough description of the GE plant could be required for review, but only minimal information regarding the conduct of the field trial.
  - An EA would not be needed as long as the field trial meets performance standards set by APHIS to ensure no significant impact.
  - Once affirmative APHIS approval is granted, planting could begin immediately.
  - A notice of issuance of the permit could be made public.
  - The permit itself, less CBI, could be made available to the public.
- The **standard review** category would be for plants that involve some environmental risk but could be planted in field trials under conditions to prevent significant environmental risk. This category could be comparable to the current field trial permitting process. Plants in this category could be handled as follows:
  - A thorough description of the GE plant and the proposed procedures to be used in conducting the trial could be required for review.
  - An EA would not be needed as long as the field trial meets performance standards set by APHIS to ensure no significant impact.
  - Once affirmative APHIS approval is granted, planting could begin 30 days after a notice is issued.
  - A notice of issuance of the permit could be made public.
  - The permit itself, less CBI, could be made available to the public.
- The **enhanced review** category could be for plants with the greatest risks, novelty, and uncertainty, possibly including plants modified to produce pharmaceutical or industrial chemicals. Plants in this category could be handled as follows:
  - A thorough description of the GE plant and the proposed procedures to be used in conducting the trial could be required for review.
  - An EA and a FONSI could be required and could be published for a 30-day public comment period. If a FONSI can't be made, an EIS would be prepared and published for public comment.
  - Proposed conditions of the permit could be published for a 30-day public comment period, concurrent with the EA and FONSI.
  - APHIS could publish the notice of decision.
  - The permit itself, less CBI, could be made available to the public.

General Release Permits

- All commercial plantings would be grown under general release permits.
- **Criteria** to be assessed for a general release permit could include the nature of the host plant, the nature of the introduced genes and protein, and the interaction of the plant with the environment.

Figure 2.4 A Tiered Permitting System for APHIS (...continued)

- Plants being considered for a general release permit could be handled as follows:
  - The developer could consult with APHIS until the agency has appropriate data and the application is complete.
  - APHIS could then publish a notice of receipt of application.
  - APHIS could then publish a draft EA and FONSI for public comment, or announce the need for an EIS.
  - APHIS could publish a notice of a proposal to grant a permit, with or without conditions, for public comment (concurrent with the EA/FONSI).
  - If the plant meets all the requirements, APHIS could affirmatively approve a permit for general release.
- Types of possible conditions on a general release permit include the following:
  - **Location or acreage restrictions.** The location or acreage of a planting could be limited, depending on the nature of the plant and its assessed risk.
  - **Permit duration restrictions.** The length of a general release permit could be varied according to the plant. While some general release permits could be unrestricted—that is, having no time limit—others could be of limited duration.
  - **Monitoring or additional data collection and associated reporting requirements.** APHIS could require post-approval monitoring and reporting as a permitting condition, and the agency would need to ensure compliance. Monitoring, when required, could be developed on a case-by-case basis, based on what is known about the product, or similar products (as opposed to an overarching monitoring program that attempts to collect data on all GE plants). In some instances, APHIS could require post-approval monitoring and reporting based on information obtained during the field trial phase and assessed during the general release permitting process; in others, the trait or crop may be sufficiently similar to one previously reviewed, approved, or assessed, such that post-commercial monitoring would be minimal or not required.
  - **Confinement requirements.** While most general release permits might not contain confinement restrictions, some permits, especially those for pharmaceutical and industrial plants, could have conditions intended to prevent them from entering the food supply.

Improving Transparency and Public Participation

One option for increasing confidence in and the clarity of APHIS's regulatory program would be to increase the transparency of and opportunities for public participation in major regulatory decisions. For example, APHIS could provide at least one opportunity for public input before any GE product could be used commercially. APHIS could also provide for public input during the development of key regulatory policies, such as performance standards for exempting an activity from an EA and criteria for the necessary studies and data to support a decision by APHIS. Permits, with CBI removed, could be made readily

accessible. The NRC report called for greater opportunities for scientific peer review and consultation with scientific advisory bodies (2002b).

If APHIS were to adopt a new tiered permitting approach, it could build in greater transparency and opportunities for public participation. For example, APHIS could provide notice of all permits, listing the characteristics of the plant and in what state, if not county, it is to be grown. This requirement should not be onerous, since similar information is currently made available by APHIS for many field trials[61] and could be posted on APHIS's web site or otherwise publicly disclosed. New APHIS regulations could require that a notice of availability of any EAs be published in the *Federal Register* at least 30 days prior to any FONSI and/or record of decision being signed concerning the issuance of a permit, which, under this rubric, would likely be either an enhanced review field trial permit or a permit for general release. This would allow the public an opportunity to comment on the EA and identify any risks that are not addressed in it, before any decision becomes final.

In a new tiered permitting system, APHIS could require peer review and consultation with outside experts on decisions involving the issuance of permits for plants in a high-risk category. APHIS could also develop a policy as to when and under what circumstances a scientific advisory panel would be asked to provide advice on a new type or category of GE plant. The panel could analyze the new category and give expert advice as to what new issues, if any, the new line presented, along with expert advice as to how to mitigate to a negligible level any new plant pest, environmental, or public health risks that are identified.

New regulations could also spell out conditions for the issuance of any permit when certain risks are identified. The regulations could describe what the standard restrictions would be and how they would be applied, so that the public would know what conditions or types of conditions were being required and why they were being required in certain situations.

APHIS could more clearly articulate what information will be protected as CBI and what information will be made public in the issuance of any permit for a field trial or general release. To the extent that it can do so within the law, APHIS could adopt policies and practices to make as much health and safety information publicly available as possible. APHIS could hold final decision-making authority regarding what information is CBI and what is not, and an applicant's failure to agree to the disclosure of certain information that APHIS determines is not CBI could mean that the applicant would have to withdraw the request to protect the non-CBI information. The applicant could have to justify claims of CBI in writing, when the application is submitted.

While additional transparency and opportunities for public participation can increase confidence in agency decisions, they can also increase costs and slow product approvals. APHIS would need to carefully weigh these trade-offs in considering changes.

Potential PPA-Related Legislative Reforms

New regulations under the PPA should be able to address most of the key issues raised regarding APHIS's current regulations and how they are implemented and enforced by

61 See www.nbiap.vt.edu for an updated list of field trial permits and notifications.

the agency. If it is deemed desirable to remove all possible gaps and uncertainties about APHIS's authority, the PPA could also be amended by Congress to clarify that APHIS has the authority to regulate all GE plants and to use any of the risk assessment, risk management, and remedial tools available under the PPA to do so. Such an amendment would preclude APHIS from having to prove that each GE plant is a plant pest or noxious weed.

Furthermore, the PPA has not entirely resolved the respective roles of the federal and state governments regarding the regulation of GE plants. The PPA does not appear to expand the authority of APHIS to regulate intrastate activities without the declaration of an extraordinary emergency.[62] Nor has the PPA made it any easier for APHIS to make required findings before it can declare an extraordinary emergency (7 USC § 7715). If an analysis of the federal-state partnership raises concerns about the ability of regulatory agencies to effectively respond to unanticipated risks or crises involving GE plants,[63] or if several states begin regulating GE plants in inconsistent (or diametrically opposed) ways, a few approaches could be taken. The PPA could be amended to clearly state that all GE plants are in, or *affect,* interstate commerce. The amendment could go on to state that it is thus necessary for APHIS to regulate all movements, or releases into the environment, of GE plants in order to protect agriculture, public health, and the environment. This change of the standard from an "interstate movement" theory to an "affect on interstate commerce" theory would make it clear that the agency can regulate all movements or releases of GE plants into the environment.

Also, as noted previously, the PPA contains no clear environmental decision-making standard; APHIS currently has no direction from Congress as to how to weigh environmental risks against other factors. Legislation could provide a standard, perhaps similar to the "no unreasonable risk" type of standard found in other laws (e.g., FIFRA; 7 USC § 136(x)). Such a standard would clarify the basis upon which APHIS would make decisions concerning the release of GE plants into the environment. Also, such a standard, if created through legislation, would clearly establish the Congressional intent that the PPA allows for risk-benefit balancing in its regulatory process, unlike the "not a plant pest" or "not a noxious weed" determinations that APHIS must currently make under the PPA.

In addition, an amendment to the PPA could be added to ensure that APHIS can deny the issuance of a new permit based on violations of, or the failure to properly follow, previously issued permits.[64]

A more dramatic option would be for Congress to provide direct authorization for APHIS to review the potential environmental impacts of plants based on the novelty of traits, instead of their "plant pest" or "noxious weed" qualities. A novel traits approach would

62 The PPA authorizes APHIS to control 'movement in interstate commerce' (7 USC §§ 7711 and 7712); the term 'movement' is defined as including "release in the environment" (§ 7702(9)). These provisions could be interpreted to give APHIS general authority only over those "releases into the environment" that are also in interstate commerce.

63 Some issues are explored in Taylor and Tick (2003), but more research needs to be done on this regulatory nexis and its strengths and weaknesses in the regulation of GE plants and food.

64 It is not clear that APHIS currently has the authority to deny permits on the basis of past permit violations. While APHIS may be able to rewrite their rules to accomplish this, the agency's authority is not clearly established in law, and therefore legislation may be necessary.

constitute a very different approach than the current system and could include novel plant varieties developed through conventional breeding as well as through biotechnology. As the National Research Council has concluded, there is no strictly scientific reason to exclude novel conventionally bred crops from a review of potential environmental harm (NRC 2002b). Canada has adopted a regulatory system that reviews novel plants for both environmental and food safety concerns.[65] While a "novel traits" approach has a certain logical consistency, it would mark a clear expansion of the regulatory review process to include plants that historically have been introduced into the market with little regulatory oversight. Such an approach would likely generate significant debate.

THE EPA

Three types of options are described here: rethinking the 10-acre exemption for EUPs, providing direct authority to enforce planting restrictions, and clarifying the EPA's authority under TSCA over GE plants and products.

Rethinking the 10-Acre Exemption for Experimental Use Permits under FIFRA

As mentioned earlier, current FIFRA regulations allow an exemption from the EUP process for GE plant researchers conducting field tests of PIPs that are 10 acres or less, provided that they meet certain conditions. Since even PIPs grown in small-scale field trials pose some risk to the food supply (and agricultural markets) due to potential cross-pollination and mishandling, the EPA could reconsider this exemption. The agency could require notification, impose more conditions on the exemption, or withdraw the exemption altogether. It could accomplish these changes through administrative means, without the need for legislation. Also, concerns about the adequacy of the oversight of these field trials could be addressed through greater coordination between the EPA and APHIS.

Providing Direct Authority over Growers

As discussed previously, the unique nature of this pesticide enforcement issue is derived from the fact that bags of seed do not carry pesticide use labels, and thus planting violations are not enforceable by the EPA. Only PIP registrants and seed companies are directly liable to the EPA, not growers. However, treating seeds as pesticides would impose illogical and onerous reporting requirements on farmers. If grower compliance is or becomes a concern for the EPA and state regulators, the EPA may need to consider administrative options to bring on-farm planting restrictions for GE seeds under more direct EPA oversight and enforcement. If the agency does not have adequate administrative alternatives to do this, it would need to seek additional authority from Congress.

Clarifying TSCA Authority over Plants Containing PMIPs

As noted previously, there is an initial question of whether a whole living organism, such as a plant, meets the definition of chemical substance under TSCA (15 USC § 2602(2)). The EPA could clarify its own interpretation of TSCA, but whether its interpretation would be

65 See http://www.inspection.gc.ca/english/plaveg/bio/pntchae.shtml for an outline of the regulation of plants with novel traits in Canada.

upheld if challenged in court is open to question. Even if the EPA does not have jurisdiction over whole plants, it may be able to claim authority over the genetic constructs and the chemical substances produced in the plants, much as the agency has asserted authority over the genetic constructs and the pesticidal proteins produced in plants modified with the *Bt* gene. To come under TSCA, however, a plant-expressed chemical substance would need to meet the definition of a "new" chemical substance or constitute a significant new use of an existing chemical substance.

If the EPA's authority is limited solely to new chemical substances produced by GE plants after such products have been extracted from the plants, the agency is likely to regulate these in the same manner as other chemical substances; new regulations would not appear to be necessary. If, however, the EPA wanted to regulate the production of the chemicals in growing plants, or argue that the plants themselves are new chemical substances, it would likely need to develop new regulations to address the unique aspects of plant-made industrial products. The agency could develop regulations requiring a "plant commercial activity notice" (PCAN) akin to those for MCANs, which lay out the scope and requirements for microbial GE products (40 CFR Parts 700, 720, 721, 723, and 725). Like the MCAN rules, any PCAN regulation would have to articulate the limits and boundaries of what, if anything, qualifies for the research and development exemption in TSCA. (For conventional chemicals, small-scale research and development activities are generally exempt from premanufacture notice requirements (15 USC § 2604(h)(3))). The regulation would also have to include a definition of covered commercial activities, a modification of the research exemption, and a definition of what is being regulated (the whole plant, or the part of the plant that makes or becomes the industrial chemical product). Except for on-site, closed greenhouse types of activities, the regulation could require a notice to the EPA before field-testing an industrial GE plant. The regulation could also indicate what kinds of data the EPA would look for in evaluating the application, and lay out an expected timeline and the steps to be taken in reaching a decision.

The EPA would likely use significant new use rules to attempt to control the increased production of regulated PMIPs. Intended future uses and production volumes are not always predictable. Once a substance is on the EPA's inventory, there are no production limitations unless a SNUR is in place (or other restrictions are imposed by regulation). SNURs are attractive since they attempt to guarantee that a new submission would be required if certain triggers or thresholds for developing the PMIP are reached (e.g., if a manufacturer were to expand the use(s) of an industrial chemical into consumer markets, or significantly increase its production volume).

As the EPA gained experience in the regulation of industrial GE plants, it might apply an innovation used in its conventional chemical PMN program. In the PMN program, the EPA has developed a kind of decision guide attempting to articulate the agency's decision logic and criteria for the approval of conventional chemical PMNs. The goal is to provide regulated entities with a guidebook or set of decision rules that the EPA uses internally for evaluating PMNs (including "red flags" or possible concerns). This has been well received by regulated entities, some of which have adopted it as in-house criteria in an attempt to accelerate the review times of new submissions. The approach not only speeds up EPA review times with lower resource costs, but it also encourages submitters to engineer into their innovation processes more environmentally friendly technology development.

The EPA's PMN program uses a tiered approach for conventional chemicals. Certain classes of chemicals are exempted (e.g., most high-molecular-weight polymers), while others are placed in different categories of increasing scrutiny depending on the kind of chemical or the characteristics exhibited. TSCA provides authority to impose testing requirements for categories of compounds, and the EPA could thus designate a tiered approach of varied testing requirements for PMIPs. The agency would have to identify what data would be appropriate for different kinds of PMIPs depending on their intended use patterns or production methods.

As noted previously, however, it is uncertain if TSCA applies to whole plants, and plant-made products would be covered only if they fell within TSCA's definitions of "new chemical substance" or "significant new use." Further, the exemption of tobacco may apply not only to plants, but to chemicals produced by the plants. To the extent that it is desirable to have the EPA review all plants engineered to produce industrial chemicals, Congress may need to provide the agency with additional authority.

Alternatively, APHIS may have authority over plants engineered to produce industrial chemicals, although its authority would be more clear if it chose to adopt new regulations under the PPA that include its noxious weed authority. As long as APHIS's authorities are sufficient to regulate the broad environmental impacts of these plants and to keep all field trials and commercial plantings of them isolated from other crops, and the FDA has sufficient ability to assess and oversee the food safety risks of any industrial chemical uses grown with a food-crop platform, the EPA's TSCA authorities could be directed solely toward assessing and ensuring the safe commercial use of the new industrial products that are derived from these plants.

Regulating Genetically Engineered Crops and Foods for Food Safety

Scientific reviews have generally found that the use of genetic engineering to modify food crops is unlikely to raise any unique food safety concerns that could not also be posed by conventional breeding techniques (NRC 1987 and 2000). While the nature of the risks is not unique, however, genetic engineering does enable plant breeders to use genes from virtually any other organism, dramatically expanding the genetic palette available. In some cases, the genetic material and its expressed proteins may not previously have been found in food. This wide range of genetic material, and the relative lack of experience with novel genes and their proteins, are the principal justifications that federal regulatory agencies use for their increased oversight of genetically engineered (GE) crops and foods (FDA 1992).

The Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) share responsibility for the safety of food derived from GE crops. The FDA has general responsibility for food safety issues that might be posed by food derived from GE crops (OSTP 1986). The EPA has responsibility for food safety regarding pesticidal substances produced by some GE crops to resist insects (40 CFR Parts 152 and 174).

This chapter reviews the federal regulatory system governing food safety, as it applies to GE crops and foods. It contains four sections. The first is a brief summary of some of the key issues under debate regarding the safety of food products derived from GE crops. The second describes the FDA's and the EPA's existing regulatory systems regarding food safety, and how those systems apply to GE products. The third section describes in detail the key issues and concerns regarding the existing regulatory system. And the fourth section outlines possible approaches—both administrative and legislative—for addressing those issues and concerns, should policy makers decide that reforms are needed.

Overview of Key Issues

Genetic engineering, like other forms of breeding, can change the composition of food in a number of ways that could affect safety.

- **Unexpected effects.** The insertion of genetic material can sometimes result in unexpected changes. For example, the genetic material could inactivate a host gene or alter control of its expression. Or, the gene product could interact with other metabolic processes in an adverse way.
- **Naturally occurring toxicants.** Many food plants contain natural toxicants that are used to ward off pests, but these toxicants often exist at such low levels that they cause no harm in food or can be removed in processing. Genetic modifications can inadvertently increase the level of naturally occurring toxicants or cause the expression of a new toxicant.
- **Nutrients.** Genetic modifications can change the level of nutrients or alter their form to make a food crop less or more nutritious.

- **New Substances and Allergens.** Genetic engineering permits breeders to insert novel genes (and their expressed proteins) into food crops that could significantly differ from the proteins that ordinarily are found in food. Such substances could affect nutrients or have toxic or allergenic properties.
- **Antibiotic Resistance Markers.** Genetic engineering involves the use of genetic markers, including antibiotic resistance markers, to help breeders determine which plants have taken up the intended genetic change. To the extent those markers are included in the genetic material in the food, it is possible they could make enzymes that would inactivate antibiotics taken orally.
- **Adventitious Presence of Nonfood Substances.** Genetic engineering is being used to modify crops so they can make industrial and pharmaceutical chemicals. While such plants are not intended for the food supply, the accidental mixing of these crops with food crops (i.e., their adventitious presence in the food supply) might occur if strict containment procedures are not followed (FDA 1992).

In many cases, these issues can also arise with conventional crop breeding, and breeders have well-established practices to test for and eliminate new varieties that have undesirable qualities (FDA 1992).[1]

The FDA's responsibility for food safety comes from the federal Food, Drug, and Cosmetic Act (FDCA; 21 USC § 301 et seq.).[2] Based on long experience, whole foods are assumed to be safe and do not require FDA pre-market review for safety. The FDA has post-market authority to remove foods from the market if they are "adulterated"—that is, if they accidentally contain a substance that "may render" the food injurious to health (FDCA § 402(a)(1); 21 USC § 342(a)(1)). However, "food additives"—substances that are *deliberately* added to foods—must be approved by the FDA as safe before they can be marketed, unless they are "generally recognized as safe" (GRAS; FDCA § 409; 21 USC § 348).

For foods derived from GE crops, the FDA's policy is that new proteins introduced by genetic engineering are likely to be "substantially equivalent" to proteins already found in food and therefore are presumed to be generally recognized as safe (FDA 1992, 1997a, and 2001a). As a result, GE foods generally do not require pre-market approval by the FDA. However, the FDA encourages biotechnology developers to voluntarily consult with the agency before bringing GE products to market (FDA 1992 and 1997a). In the consultation process, the FDA reviews summaries of safety testing conducted by the manufacturer and, if satisfied, provides the manufacturer with a letter stating that the agency has "no further questions" and reminding the manufacturer that safety is the manufacturer's responsibility (FDA 1997a). In 2001, the FDA proposed making this pre-market consultation mandatory, but it has not acted to finalize that proposal (2001a). The FDA believes that it has reviewed, under the voluntary process, all GE foods currently on the market (2001a).

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1 In its 1992 policy guidance statement, the FDA noted that the same safety issues posed by biotechnology can be posed by conventional breeding techniques as well. It cited the case in the 1970s of a new, conventionally bred variety of potato that was found during its development to contain elevated and potentially harmful levels of solanine, a naturally occurring toxin, as a result of a cross with an inedible wild potato.

2 Note that the U.S. Department of Agriculture regulates the safety of meat, poultry, and egg products (21 USC §§ 601 et seq., 451 et seq., and 1031 et seq.).

The EPA reviews the safety of pesticidal substances produced by some GE crops under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA; 7 USC § 136 et seq.). These GE substances are know as "plant-incorporated protectants" (PIPs). The EPA also sets "tolerances" or gives exemptions from tolerances for pesticide residues in food under the FDCA (21 USC § 346a), which states that a food is illegally adulterated if it contains pesticide residues that exceed the EPA's tolerances. (Note that the EPA's regulatory system is only touched on briefly in this chapter, as it was discussed fully in Chapter 2.)

A major issue under debate regarding the food safety of GE products is the lack of a mandatory pre-market approval process for GE foods under the FDA's current policy. Critics of the current system argue that reliance on voluntary pre-market consultations and the FDA's post-market enforcement authority is inadequate to ensure that GE foods coming to market are safe, particularly in light of future products that are likely to be more complex and pose more difficult safety questions. Critics also argue that the current voluntary system is unlikely to instill consumer trust in the regulatory system. Others argue to the contrary that the current system has worked well, without safety problems, and has adequate flexibility and authority to deal with any future problems that may arise. They also note that, as a practical matter, industry considers consultation with the FDA to be a mandatory process and that all GE foods commercialized to date have been reviewed by the FDA for safety. This report lays out a number of options to achieve the goal of a mandatory pre-market approval process, should policy makers determine that a change is desirable. The options consider both existing agency authorities and new legislation. Arguments for and against each of the options are included.

A related issue involves the adequacy of the regulatory system to ensure the safety of food that contains low levels of substances produced by experimental or nonfood-use GE crops. Nonfood-use GE crops are those that have been modified to produce nonfood substances, such as pharmaceuticals and industrial chemicals. These substances are sometimes referred to as "plant-made pharmaceuticals" (PMPs) and "plant-made industrial products" (PMIPs). Currently the Animal and Plant Health Inspection Service (APHIS) of the U.S. Department of Agriculture (USDA) regulates field trials of such GE crops to minimize the possibility of their mixing with crops intended to be used as food or feed (APHIS 2003c); the EPA also oversees experimental field trials of GE plants that produce PIPs. However, neither APHIS nor the FDA has clear responsibility for assessing potential food safety concerns at the stage where experimental or nonfood-use crops are being grown. Critics argue that APHIS's field trial requirements are unlikely to prevent some mixing of experimental or nonfood-use GE crops with food crops. This report reviews a number of policy options for achieving an early food safety assessment of experimental and nonfood-use GE crops, as well as arguments for and against each option.

The Existing Regulatory System

This section describes the FDA's authorities under the FDCA (21 USC § 301 et seq.) and the EPA's authorities under both FIFRA (7 USC § 136 et seq.) and the FDCA (21 USC § 346a). The section concludes by addressing an emerging issue—that of the possible adventitious presence in the food supply of low levels of GE crops that are not intended for the food supply, such as crops that have been bioengineered to create pharmaceuticals or industrial chemicals. The authority of APHIS and the FDA to address this issue is discussed.

THE FDA

This section describes first the basic food safety approach used by the FDA under the FDCA. It then explains how that approach is applied to GE foods.

The Food Safety Provisions of the FDCA

The safety of whole foods has been established through long human use, and food producers may introduce novel varieties of whole foods to the market without any prior FDA review or approval. Under the FDCA, the FDA does not have the authority to require pre-market approval of whole foods; it is the marketer's legal responsibility to ensure the safety of the food. The FDA's historical approach to food safety is to rely on post-market enforcement against unsafe foods. The agency can seize adulterated food, enjoin its distribution or sale, and refer offenders for criminal prosecution. Under the law, food that is "adulterated" is defined as containing a naturally occurring substance that is "ordinarily injurious" to health (such as a poisonous mushroom) or an added substance that "may render" the food injurious to health (FDCA § 402(a)(1); 21 USC § 342(a)(1)). Typically, this latter authority is used to regulate levels of unavoidable environmental contaminants in food, but it could also be applied to a new variety of food that contains potentially harmful levels of naturally occurring toxins (FDA 1992). In an enforcement proceeding, the agency has to prove that an added substance creates a "reasonable possibility" that consumption of the food would be harmful (*United States v. Lexington Mill & Elevator Co.,* 232 U.S. 399 (1914)). As a practical matter, the very threat of an FDA proceeding often results in a manufacturer voluntarily removing the suspect food product from the market.

Substances intentionally added to food are treated under different rules. In 1958, Congress amended the FDCA's Section 409 (21 USC § 348) to address the use of "food additives," defined as any substance whose intended use results in its being a component of food or affecting the characteristics of food, if the substance is not generally recognized as safe (FDCA §§ 201(s) and 409; 21 USC §§ 321(s) and 348). Under this section of the law, new food additives, unlike new whole foods, need to be approved by the FDA before they can be marketed; a food that contains an unapproved food additive is considered to be adulterated and is illegal to market (FDCA § 402(a)(2)(c); 21 USC § 342(a)(2)(c)). The sponsor of a new food additive has the burden of showing that it is safe, which the FDA defines as presenting a "reasonable certainty of no harm" (21 CFR § 170.3(i)). The safety of an additive is established through a formal FDA rulemaking proceeding, at the end of which the FDA may issue a rule setting out conditions for the safe use of the food additive (21 CFR § 171.1). (See Figure 3.1).

By definition, however, a substance added to a food is *not* a food additive if it is GRAS. Under the FDCA, a substance is GRAS if there is a general consensus among informed experts that the substance is safe. Safety must be shown from publicly available information, including, for new additives, the same scientific procedures required to assess the safety of a food additive (FDCA § 201(s); 21 USC § 321(s)). The FDA has published regulations listing food ingredients that it has found to be GRAS for specified purposes and conditions of use (21 CFR Part 184); however, the agency has always maintained that its GRAS list is not comprehensive (FDA 1992). Significantly, the result is that companies are free to make their own independent GRAS determinations and to market substances on that

Figure 3.1 The Food Additive Petition Process

The **food additive petition process** differs from the informal rulemaking process typically used by agencies to issue regulations under the Administrative Procedures Act (5 USC § 553) and has been criticized for being slow and cumbersome (Noah and Merrill 1998). A developer normally initiates FDA action through a food additive petition. The FDA publishes a notice in the *Federal Register* once such a petition has been filed. At that point, the petition is subject to disclosure under the Freedom of Information Act (5 USC § 552 et seq.). (In 1974, the FDA determined that safety information contained in food additive petitions should be made publicly available.) While not required by law or regulation, the FDA tacitly accepts pre-approval public comments at this point in the process (Noah and Merrill 1998, 371). The petition is required to contain information identifying the substance's proposed use (through labeling), all relevant data concerning its effect on food, all safety studies, and residue detection methodologies. Since the petitioner must carry the burden of proof to demonstrate a "reasonable certainty of no harm," such evidence can be extensive, and the FDA can request supplementary data (21 CFR § 171.1). The petition also must include either an environmental assessment or a claim of categorical exclusion from the National Environmental Policy Act (21 CFR § 171.1(c)). The FDCA requires the FDA to act on the petition within 90 days, or within 180 days if the agency requests an extension. However, this deadline is almost never met (Noah and Merrill 1998, 373). When the agency does issue a final order denying or granting approval of the petition, any person "adversely affected" by the order may file objections thereto within 30 days and request a formal evidentiary hearing. In the FDA's history, only two direct food additives have been the subject of formal hearings (Noah and Merrill 1998, 374). According to food processors, the average cost for a food additive petition ranges between $15 million and $25 million, and in several instances has exceeded $200 million (cited in Noah and Merrill 1998, 375). Unlike other FDA regulatory approvals, the approval of a food additive petition operates as a public regulation that allows any person, not just the petitioner, to sell or use the food additive for the purposes approved by the FDA.

basis.[3] However, marketers do run the risk of enforcement proceedings if the FDA disagrees with their self-determinations.

In an enforcement action, the FDA is required to prove that the substance is an unapproved food additive. As a practical matter, that burden may not be difficult to meet. The FDA can show, for example, that there is no general agreement among knowledgeable experts that the substance is safe, or that there is no meaningful, publicly available scientific data supporting safety. The FDA would not need to show that the substance is harm-

3 Since 1997, the FDA has stopped affirming the GRAS status of substances and instead encourages companies to submit a voluntary pre-market notification setting forth the basis for a company's determination that a substance is GRAS. The FDA responds to each notification with any objections they may have, but does not make a finding as to the GRAS status of the substance. Thus, the manufacturer remains responsible for the GRAS determination and according to the FDA must carry the burden of proof of safety in court (FDA 1997b).

ful.[4] A marketer faced with the threat of an FDA enforcement action will in many cases voluntarily remove its product rather than face the adverse publicity of enforcement.

The FDA's Policy on Foods Derived from GE Plants

In 1992, the FDA published guidelines that set out its policies for reviewing food derived from genetically engineered crops. In that policy, the FDA reiterated its position that the safety of whole foods derived from GE crops would be judged in the same manner as other whole foods. For example, if a genetic modification *inadvertently* changed the level of a naturally occurring toxicant to a point that it could be hazardous, the toxicant would be considered an added substance that "may render" the food injurious to health, and the food would be deemed adulterated under Section 402(a)(1) of the FDCA (FDA 1992). Consistent with the statutory approach to whole foods, however, the FDA would have legal power to act only after such a product was on the market; no legal provision requires the pre-market review or approval of foods derived from GE crops.

The FDA's 1992 guidelines also stated that genetic materials and their expression products (such as nucleic acids, oils, carbohydrates, and fats) *deliberately* added to food via genetic engineering would be treated as potential food additives under Section 409. However, the agency indicated that in most cases the added substances in GE foods would presumptively be GRAS, and therefore not food additives, because similar substances were already commonly consumed in the food supply. However, added components that "differ significantly in structure, function, or composition" from substances already in the food supply could be treated as potential food additives requiring the FDA's pre-market approval.[5] The FDA also noted that changes in composition, even if they do not create a food safety issue, might need to be labeled in order to comply with the FDCA's misbranding provisions.[6]

4 Some scholars have suggested, however, that the burden of proof issue is not clear (Noah and Merrill 1998). The FDA has argued that the burden would be on the developer to prove that the substance is GRAS, and therefore not a food additive (FDA 1997b). But the burden may be on the FDA to demonstrate that the substance is a food additive, and therefore not exempt as GRAS; that burden, as noted in the text, may not be difficult to meet. In either case, a marketer would be taking a substantial risk by proceeding to market with a product about which the FDA had voiced safety reservations.

5 The FDA's decision not to treat GE foods as food additives under the FDCA was upheld as a permissible exercise of discretion in a court challenge to the agency's 1992 policy statement. The court also deferred to the FDA's position that special labeling for GE foods as class is not warranted (*Alliance for Bio-Integrity, et al. v. Shalala*, 116 F.Supp.2d 166 (D.D.C. 2000)).

6 The FDCA contains several provisions that are intended to ensure truthful and accurate labeling to avoid deception and misrepresentation. Section 403(i) of the FDCA (21 USC § 343(i)) requires that each food bear a common or usual name or, in the absence of such a name, an appropriately descriptive term. In addition, under § 201(n), food labeling must reveal "all facts that are material in light of representations made in the labeling or in light of consequences that may result from the use of the foods" (§ 321(n)). As a consequence, the FDA has indicated that a food derived from a GE crop (or any other new plant variety) would need to be labeled if it differed from its conventional counterpart to such an extent that its conventional name might be misleading, or if it involved a safety or usage issue to which consumers must be alerted. However, the FDA also determined that the fact that a product was derived from a GE plant was not a material difference requiring disclosure (FDA 1992). If a food derived from a GE plant contained an allergen, however, or differed in its nutritional composition from its conventional counterpart, that fact would need to be disclosed. (See also FDA 2001b.)

Table 3.1 FDA Treatment of Genetically Engineered Food

POSSIBLE CHANGES TO FOOD FROM GENETIC ENGINEERING	LEGAL STANDARD	FDA AUTHORITY	FDCA SECTION IN 21 USC
Inadvertent changes to whole foods	May render the food injurious to health	No mandatory pre-market review or approval; post-market authority only	§ 342(a)(1)
Deliberately added food substances that are generally recognized as safe	Generally recognized as safe	No mandatory pre-market review; if the FDA disagrees with GRAS determination, can bring enforcement action to show that the substance is an unapproved food additive	§ 348
Deliberately added food substances that are not generally recognized as safe	Reasonable certainty of no harm	Food additive; mandatory pre-market approval	§ 348
Material changes in composition or nutrition	Misrepresentation (not a safety standard)	Labeling of material facts or consequence	§ 343(i); § 321(n).

In effect, the FDA applies several different legal standards in evaluating the safety of GE foods.[7] Under Section 402(a)(1) of the FDCA, a food containing inadvertent changes caused by genetic modifications will be found to be adulterated if the unintended changes "may" render the food injurious to health. FDA enforcement of this provision, however, occurs after marketing. Under Section 409 of the FDCA, a food containing a substance intentionally added by genetic engineering (the genetic construct and its expression products) is either (1) deemed to contain a food additive, in which case pre-market approval of the food is required and the manufacturer must demonstrate that the food poses a "reasonable certainty of no harm," or is (2) deemed to be GRAS, in which case no pre-market review is legally required. A GRAS determination for genetically engineered foods focuses on whether the food is substantially equivalent, or as safe as, its non-GE counterpart (FDA 1992, 1997a, and 2001a; Maryanski 1995). (See Table 3.1.)

The FDA's 1992 policy statement also included guidance to help developers determine whether or not substances added or modified as a result of genetic engineering were food additives or GRAS, and it encouraged developers to consult with the agency prior to marketing a food derived from a GE crop in order to resolve any questions about the regulatory status of the new product. As part of the consultation process, developers are

7 To be clear, while the text here refers to 'food,' the FDA, in its consultations with biotechnology developers, considers the specific transformation event in each crop, not the various foods or food ingredients that might eventually be derived from the crop. In other words, the FDA looks at the safety of the changes in the plant itself that have resulted from genetic engineering.

asked to outline the basis for their conclusion that the components added to the food by genetic engineering are substantially equivalent to those in its traditional counterpart and therefore GRAS (FDA 1997a). (See Appendix B.) Under this consultation process, the FDA's Center for Food Safety and Applied Nutrition (CFSAN) does not conduct a comprehensive scientific review of the data submitted by the developer, but, based on agency scientists' evaluation, considers whether there are any unresolved safety issues. The FDA considers the consultation to be completed when all safety and regulatory issues are resolved. At the end of the consultation, the FDA sends a letter to the developer indicating that the agency has "no further questions" and reminding the developer that it is the developer's responsibility to ensure the safety of the product and to comply with all laws and regulations (FDA 1997a; see also CEQ and OSTP 2001). The FDA could, of course, issue a letter stating that it does have further questions about a developer's conclusion that a product is safe, but as a practical matter a developer would be more likely to simply withdraw the application than have the FDA issue a public letter questioning the product.

The FDA then places a copy of the closing letter and the agency's summary of the developer's data on its web site.[8] The information submitted by the developer to the FDA, typically a summary of data, is subject to public disclosure under the Freedom of Information Act (FOIA; 5 USC § 552 et seq.), although trade secrets and "confidential business information" (CBI) are withheld.[9] As a result, there is no public notification of the consultation until the FDA places the closing letter on its web site, nor are there any provisions for public comment.

Under this process, the FDA's letter is not a formal safety "approval" of the food by the agency; the safety of the product remains solely the developer's responsibility. In practice, however, the FDA has noted that developers routinely consult with the agency, and the FDA believes that all foods derived from GE plants currently on the market have gone through the consultation process (FDA 2001a).[10]

In 2001, following a series of public hearings, the FDA proposed to replace the voluntary consultation process with a mandatory pre-market notification process, which would require developers to notify the FDA 120 days in advance of commercial distribution of foods derived from GE crops. Under this proposed "pre-market biotechnology notification" (PBN) rule, developers would submit information to demonstrate that a bioengineered food is as safe as comparable food and that the intended use of the food is in compliance with the law (i.e., that the food and its added components are safe and do not require a food additive approval). (See Appendix B.) As with the current voluntary system, the FDA would respond with a letter to the developer, stating that it had no further questions at this time (FDA 2001a). Alternatively, the FDA could issue a letter stating that the information does not provide a basis for the safety conclusion, extend its evaluation period, or acknowledge the withdrawal of a PBN (FDA 2001a).

8 See http://www.cfsan.fda.gov/~lrd/biocon.html

9 18 USC § 1905 makes it a federal criminal offense for any federal employee to disclose trade secrets or certain other CBI not authorized by law. The Freedom of Information Act exempts from public disclosure "trade secrets and commercial or financial information obtained from a person and privileged or confidential" (5 USC § 552(b)(4)).

10 Calgene's Flavr Savr tomato was reviewed by the FDA under a voluntary food additive advisory opinion process, prior to the adoption of the 1992 policy statement (FDA 1992).

The proposed PBN rule would also institute a number of procedural changes to make more information available to the public. The FDA proposed to publish the receipt of each completed PBN, which would provide public notice that a consultation process on a specific product was on-going. Nonconfidential materials filed by the developer with the agency under the PBN would be available for public disclosure under FOIA, unless the developer demonstrated that the fact of the consultation would itself be confidential business information exempt from disclosure under FOIA. The proposed rule would not provide an opportunity for public comment on the PBN. As with the current system, the FDA would make public the text of its letter in response to the PBN and the agency's completed evaluation (FDA 2001a). To date, however, the proposed PBN rule has not been made final, and recent statements from FDA officials suggest that it is not a high priority.[11]

Between 1991 and 2002, the FDA completed 55 consultations for foods derived from GE crops. The majority of these consultations were completed in 1995 (14), 1996 (11), and 1998 (13). The FDA's web site does not list any consultations completed after October 2002 (FDA 2002b).

THE EPA

Chapter 2 contains a complete discussion of the EPA's regulatory system governing GE plants. In brief, the EPA regulates pesticidal substances expressed by GE plants. The EPA has issued regulations requiring the registration of plant-incorporated protectants, or PIPs (40 CFR Parts 152 and 174). The EPA is also responsible for issuing tolerances or exemptions for tolerances for pesticide residues in food (21 USC § 346(a)). The agency has exempted all currently registered PIPs from the requirement for a pesticide residue tolerance in food, other than StarLink corn.[12] The agency has also issued a rule that categorically exempts from the tolerance requirement all nucleic acids that are part of PIPs, since nucleic acids that compose DNA are a ubiquitous part of the food supply and raise no safety issues (40 CFR Part 174).

APHIS, EPA, the FDA, and the Issue of Adventitious Presence

Food safety issues arise not only regarding GE crops themselves, but also due to the possibility that conventional crops can become accidentally mixed with low levels of GE crop materials. Such mixing can take place if GE plants cross-breed with sexually compatible conventional plant varieties.[13] In addition, seed and grain from GE plants can become physi-

11 FDA Deputy Commissioner Lester Crawford testified in June 2003 before the House Committee on Agriculture's Subcommittee on Conservation, Credit, Rural Development, and Research that since "the current system is working so well and since there is no public health reason to impose the mandatory requirement, it is not a high priority for FDA to finalize this rule at this point" (U.S. House 2003, 16).

12 In 2000, the EPA approved StarLink corn, a variety of corn modified with *Bacillus thuringiensis (Bt)* genes to produce a toxin to kill pests, solely for animal feed use because of concerns about the possible allergenicity of the protein to humans. Despite this restriction, low levels of StarLink corn were found in a wide variety of corn-based food products, resulting in a major, voluntary food recall and a disruption of trade. The EPA had exempted feed uses of StarLink corn from a tolerance, but not human food uses; as a result, the appearance of StarLink in the human foods made such uses per se adulterated and unlawful under the FDCA (Taylor and Tick 2001). StarLink has since been withdrawn from the market and its registration is no longer active.

13 Different crops have widely different capabilities to spread their genetic material through pollen drift and cross-breeding (Eastham and Sweet 2002).

cally mixed in with seed and grain from other varieties during harvesting, storing, and transporting. As a result, pollen flow and mixing can result in unintended, low levels of GE substances in conventionally bred crops, sometimes referred to as adventitious presence. The inadvertent mixing of a GE crop with crops intended for food or feed could raise potential food safety issues if the GE crop has not been reviewed for safety by the FDA (as in the case of experimental field trials) or if the GE crop contains a pharmaceutical or industrial substance not intended for use in food. There is a general consensus that plants genetically engineered for nonfood purposes should not be used as food and that care should be taken to keep such plants and their genetic materials out of the food supply (NRC 2004; FDA 1992).[14]

This issue has taken on greater significance in light of the increasing number of food crops, such as corn, that are being modified for nonfood-use purposes. According to one recent report, APHIS has approved 344 test sites for field trials of plants genetically engineered to produce pharmaceutical or industrial chemicals (Caplan 2003). In 2002, APHIS authorized fewer than 20 field tests for plants engineered to produce pharmaceutical compounds, on approximately 130 acres at 34 sites (APHIS 2003c). The USDA estimates that approximately 60 companies and 60 research institutes are actively involved in nonfood-use crop research and development worldwide (APHIS 2003b).

To date, the focus of federal regulatory efforts has been to prevent any mixing of experimental GE crops with crops intended for use in food or feed. APHIS has primary responsibility for regulating field trials of all GE plants. (APHIS's regulatory system is discussed at length in Chapter 2.) Under APHIS's guidelines, all field trials of GE crops must be conducted in a way that minimizes the potential for gene flow and ensures the destruction of the crops at the end of the trials. In addition, APHIS has issued stricter guidelines for field trials of nonfood-use GE plants that require greater separation distances and other containment measures (APHIS 2003c). The agency also requires permits (rather than notifications) for all plantings of nonfood-use GE crops (APHIS 2003b).

The EPA also has regulatory responsibility under FIFRA for experimental field trials of GE crops modified to produce pesticidal substances, as discussed in Chapter 2. Under general pesticide laws, the EPA requires "experimental use permits" (EUPs) for field trials of greater than 10 acres. Developers conducting field trials of PIPs of under 10 acres are not required to notify the EPA nor obtain prior EPA approval, as long as they destroy any food or feed crops or, alternatively, have a pesticide residue tolerance or an exemption from a tolerance for the PIP being tested (40 CFR § 172.3(c)(1)(ii)).

The FDA usually has not reviewed the food safety of GE crops, including nonfood-use GE crops, at the field trial stage.[15] In part, this may be due to the assumption that compliance

14 In its 1992 policy statement, the FDA discussed the potential of plants modified to produce nonfood chemicals to mix with the food supply. The FDA stated, "In such cases, the developer must ensure that food-use varieties of the crop do not cross with or become mixed with nonfood varieties" and indicated that both food producers and the developers of nonfood crops have comparable obligations to avoid mixing the two crops. In addition to raising possible food safety issues, the commingling of nonfood-use GE crops and food crops could pose consumer acceptance, misbranding, and economic liability issues for food companies.

15 The FDA encourages developers to consult with the agency at the earliest possible time and has requested that developers of crops that produce nonfood substances also consult with the agency (FDA 2001a). An early consultation, if initiated by a developer, could help the FDA identify a potential food safety concern at an early stage, but a developer is likely to provide extensive safety data only after field trials are conducted and a preliminary decision is made that the product is a good candidate for commercialization.

with APHIS's containment guidelines precludes substances from experimental GE crops from getting into the food or feed supply. The Office of Science and Technology Policy (OSTP) recently called on the FDA, EPA, and APHIS to consider ways to ensure an early food safety assessment for field trials of GE crops *intended for food or feed use* (2002).

Issues and Concerns regarding the Existing System

This section analyzes a number of issues relating to the regulation of GE plants for food safety. Included are discussions of pre-market and post-market authority for foods derived from GE plants; pre-market authority for food safety concerns posed by the presence of low levels of unreviewed GE substances in food; and clarity, transparency, and public participation.

The significant question about the regulatory system for food safety is not so much whether products are covered by the system as it is the adequacy of the FDA's authority. In particular, the issue is whether it is sufficient to rely solely on the FDA's post-market authority to act against food that may be unsafe, or whether it would be desirable for the FDA to approve products derived from GE crops as safe before they go to market.

PRE-MARKET AUTHORITY FOR FOODS DERIVED FROM GE CROPS

One element in considering the adequacy of a regulatory system is whether an agency has the authority to prevent injury by reviewing or approving potentially harmful products before they go to market. As noted, the FDCA places responsibility for the safety of whole foods on marketers, and the FDA relies primarily upon its post-market enforcement authority to remove unsafe foods from the market (21 USC § 342(a)(1)). Only food additives are subject to a mandatory pre-market approval process, but substances added to food that are GRAS are not considered to be food additives (§ 348). Under the FDA's 1992 policy guidance, the materials added to foods through biotechnology are presumed to be GRAS because of their similarity to substances already found in food.[16] As a result, the FDA does not have the legal authority to require mandatory pre-market approval of substances added to food through genetic engineering in food crops, except in cases where those substances may warrant food additive status.

Some GE foods, regulated under different legal provisions, are currently subject to mandatory pre-market approval. PIPs in GE crops are regulated by the EPA under FIFRA and the FDCA and must be found by that agency to pose "a reasonable certainty of no harm" in food before they are permitted on the market (§ 346a(b)(2)(A)). As discussed in Chapter 4, the FDA's Center for Veterinary Medicine may decide to approve the safety of meat from genetically engineered animals, including fish, under the FDCA's new animal drug approval authority, which includes a mandatory pre-market approval (CEQ and OSTP 2001).

16 In its 1992 policy statement, the FDA made a scientific determination that the materials deliberately added to foods through biotechnology are presumptively GRAS because of their similarity to substances already found in the food supply. The agency would have a heavy burden to justify changing this position. Where, as here, the agency's previous determination was a scientific one, and not just a policy preference, the agency would need to justify a change on the basis of new scientific information. In the absence of new information that supports a different conclusion, making such a finding would likely not survive a legal challenge (see *Motor Vehicles Mfrs. Ass'n v. State Farm Mut. Aut. Ins. Co.*, 463 U.S. 29 (1983)).

As discussed in more detail below, some believe that a mandatory pre-market approval process is needed for future bioengineered crops, both to ensure an adequate review of possible food safety risks before those crops go to market, and to build public trust in the regulatory system. Others believe, pointing to a 10-year history of GE food use without a major food safety problem, that the current system provides adequate protection.

Arguments that Mandatory Pre-Market Approval Is Needed

Arguments supporting the need for a mandatory pre-market approval system for food safety are summarized below. These arguments do not necessarily represent the authors' opinions.

The lack of a legally mandatory process and an affirmative approval of safety by the FDA fails to protect against potential food safety problems and undermines the credibility of the regulatory system. The FDA cannot impose legal penalties on companies for failing to get pre-market approval for GE foods, so the agency relies on the cooperation of companies to ensure that it reviews GE crops for possible food safety issues before they go to market. Unless there is cooperation, the FDA has no way of knowing what products have gone to market unless and until a safety issue becomes apparent after a product is on the market. Although this situation has not caused a problem to date, as the industry has apparently been fully compliant, it could become more of a problem in the future when GE crops created in other countries are imported into the United States, as the FDA acknowledged in its 2001 PBN proposed rule.[17]

In addition, future food products of biotechnology are likely to have novel traits and more complex genetic modifications that will raise more difficult safety issues than were presented by the current generation of GE crops, a concern that the FDA also cited as a justification in its 2001 PBN rule.[18] *Given the novelty of genetic transfers and the lack of experience with them in the food supply, it is appropriate to subject them to more scrutiny than new varieties produced through conventional breeding. While all GE crops should be reviewed, the level of review of each product should be proportionate to the risks it presents. As the agencies gain experience and science improves, genetic transfers that are well understood and present low risk should be given expedited reviews and approvals, while novel and more complex products that could pose risks should be given appropriately greater scrutiny. As a result, a properly structured mandatory pre-market approval process need not be more time consuming nor burdensome for many GE products than the current voluntary system. Given these issues, the FDA should prevent possible harm by approving the safety of future GE foods before they go to market rather than relying solely on post-market authority to respond to problems after they occur.*

17 The FDA noted in 2001 that approximately 45% of the plant-derived food in the United States is imported, and that percentage continues to increase. The agency expects that rDNA techniques may, over time, be used increasingly by plant breeders and developers in countries that export foods to this country. In such circumstances, the FDA stated: the "accuracy of the FDA's knowledge about the presence in the U.S. food supply of foods using rDNA techniques is likely to decrease" (2001a, 4712). Provisions since enacted by Congress could help increase the FDA's awareness of imported foods; see Title III of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (PL 107-188), which requires advance notice of imports and increases the FDA's inspection and enforcement authorities for food imports.

18 The FDA noted that the current commercially available GE crops represent "only a small fraction of the potential products of rDNA technology" and that future products in the development pipeline are "more likely than in the past to raise regulatory issues falling under FDA's purview" (2001a, 4711).

A mandatory pre-market approval process would also give the FDA more leverage to request and obtain safety data from developers by keeping products off the market until the agency is satisfied that they are safe. In addition, food companies may find an FDA determination of safety to be a legal shield against possible liability claims. The current voluntary system, which lacks an affirmative safety finding by the FDA, provides no "safe harbor" for the food industry should a food safety issue caused by a GE food product arise. Also, a mandatory pre-market approval system makes it much easier for the FDA to enforce its rules. In an enforcement proceeding, the FDA would need only show that a food lacks the required FDA approval; it would not need to demonstrate that the food might be harmful. In other words, taking an unapproved food to market would be per se illegal. In contrast, in a post-market enforcement proceeding under 21 USC § 342(a)(1), the FDA would need to show some possibility of harm from the food, a burden that could be difficult to meet (Noah and Merrill 1998, 334).

In addition to providing the authority needed for ensuring public health, a mandatory pre-market approval system for future GE foods is needed to create public trust in the regulatory system. A regulatory system that fundamentally relies upon the voluntary cooperation of the industry being regulated is unlikely to be perceived as being as credible as a rigorous, independent, and mandatory review. Moreover, a determination of safety by the FDA, based on a review of a full range of data, is likely to be viewed as far more credible on the issue of safety than a statement by the FDA that it has "no further questions" after reviewing a summary of information prepared by a developer, particularly if the safety determination process provides for more transparency and an opportunity for public participation. Finally, a mandatory pre-market approval process for all future GE foods is a clear and straightforward process that could be understood by the public and the industry alike, without the legal uncertainty and complexity of the current system. The greater credibility of a mandatory pre-market approval process is more likely to help serve the commercial interest of building consumer confidence in the technology itself.

Arguments that Current Review Is Adequate

The following is a summary of arguments that the current food safety oversight system is adequate to ensure safe food. As before, the opinions expressed are not necessarily those of the authors.

The FDA's current policy is adequate, as shown by the safe record of bioengineered foods that are currently on the market; there is no evidence that these foods have caused any food safety problems. Without known exception, developers of all of the GE food crops have been through the FDA's current review process. While the system is not mandatory in the sense that developers are not subject to legal penalties for noncompliance, the reality is that the market would reject any GE crop that had not received a "no further questions" letter from the FDA, and, as a consequence, FDA review is "mandatory" in a practical sense.[19] *Developers believe that they have no practical alternative to providing the FDA*

19 Lisa Dry, a representative of the Biotechnology Industry Organization, stated that food processors need the FDA's "no further questions" letter issued at the end of the voluntary consultation process to do business. "They treat it as though it were mandatory," she said, "because if they don't, they won't get a letter of review so that they can sell their product" (AP 2003).

with any information that it requests in order to receive the "no further questions" letter. As a result, the FDA has an adequate opportunity to identify any potential food safety issues before a GE crop goes to market, and the information that it requests from companies to assess safety is sufficient to identify any food safety risks. If a developer goes to market with a GE food that includes a substance that it claims is GRAS, but that the FDA believes raises a food safety concern, the FDA's burden of showing that the substance is not GRAS but rather an unapproved food additive should not be difficult to meet. The FDA has a successful record of using its post-market enforcement authorities, and the very threat of a possible enforcement action can often lead to the prompt "voluntary" recall of food suspected of being unsafe. Furthermore, because of the consultation process, GE crops receive more pre-market regulatory review than novel varieties of conventionally bred crops.

In addition, with respect to more complex GE food products, the FDA has adequate authority and flexibility to subject foods that do not meet the GRAS test to the pre-market approval requirements of the food additive process. There is no scientific justification for treating new varieties of food derived from GE crops any differently than novel varieties from conventional breeding, which have largely been considered GRAS. In particular, subjecting all GE crops to a mandatory pre-market approval process reverses the long-established policy that regulation should be based on the risks of the product, not on the process by which it is made. Finally, the public currently has confidence in the FDA and the safety of the food regulatory system. (See, for example, PIFB 2003).[20]

POST-MARKET AUTHORITY FOR FOODS DERIVED FROM GE CROPS

Another criterion for judging the adequacy of a regulatory system is whether an agency has the authority to impose restrictions or conditions on a crop once it is in the field or on the market, monitor compliance with those restrictions, obtain data if unexpected adverse events occur, and respond to problems if they occur.

The EPA has broad authority under the pesticide laws to impose post-approval conditions on the use of pesticides (40 CFR § 174.71) (See, Chapter 2 for a discussion of EPA's post-market authorities). The FDA has similarly broad post-approval authority to ensure the safe use of food additives. The FDA can require labeling and use restrictions as a condition of its approval of a food additive and has negotiated agreements to collect post-approval data.[21] The FDA may bring an enforcement action against the unapproved use of a food additive by showing that the use violates the terms of the food additive rule.

For whole foods and for products introduced into commerce under the GRAS exemption, however, including foods derived from GE crops, the FDA has no monitoring program in place nor any practical way of knowing what products are being introduced into the mar-

20 In this poll, 83% of those surveyed responded that they trusted the FDA "some" or a "great deal" for information about genetically engineered foods.

21 In the case of Proctor & Gamble's olestra, for example, the FDA imposed labeling requirements and required foods containing the ingredient to be fortified with certain vitamins. There is some legal question whether the FDA can impose post-market data collection requirements; in this case, Proctor and Gamble entered into a voluntary agreement to collect certain post-market data (Noah and Merrill 1998, 418-419).

ketplace (Taylor and Tick 2003).[22] The FDA has no authority to place restrictions on the marketplace use of such foods except through the use of its post-market powers under 21 USC § 342 to seize, enjoin, or bring criminal actions against foods that it can show are adulterated. The agency can also use its separate authority to police misleading labels to require disclosures if a food product has been modified in a way that might mislead consumers about its composition or quality (21 USC §§ 201(n) and 343(i)). New powers given to the FDA by recent bioterrorism legislation may provide additional post-market authorities in cases of significant public health risks.[23]

As with mandatory pre-market approval, a range of opinion exists with respect to the adequacy of the FDA's post-approval authority for future biotechnology products. Some argue that, to the extent the agency's current voluntary consultation process is adequate to ensure the safety of bioengineered foods, the lack of a post-market monitoring and data collection program and the agency's inability to impose conditions on the marketing of foods are unlikely to pose any food safety issues. Others suggest that the development of new traits in food crops that are not intended for the food supply—e.g., pharmaceutical and industrial applications, as well as GE "designer foods" that are developed to address special nutritional or dietary needs—may create a need for the FDA to apply special use restrictions and requirements to ensure that such new products do not pose a risk to the general food supply.

PRE-MARKET AUTHORITY FOR FOOD SAFETY RISKS FROM THE ADVENTITIOUS PRESENCE OF UNREVIEWED SUBSTANCES IN FOOD

The current regulatory system relies on APHIS's notification and permitting system to both contain field trials of experimental GE plants, including those that are intended to produce pharmaceutical or industrial chemicals, and prevent the spread of unreviewed genetic material to food crops. In the event that mixing nevertheless occurs, the FDA can use its post-market authority under 21 USC § 342(a)(a)(1) or (2) (and possibly Section 348) to take action to remove unsafe foods from the market.

The question is whether any agency has the authority or responsibility to review GE crops for food safety concerns *before* they are planted, in case complete containment fails or low levels of mixing are unavoidable. It is not clear whether either APHIS or the FDA has clear authority or responsibility to address such issues before the crops are grown experimentally or commercially. The EPA does appear to have authority, but only over GE crops that produce pesticidal substances.

APHIS grants permits for field trials of GE crops under regulations that are based on its legal authority to regulate and control potential "plant pests" (7 CFR Part 340). Its author-

22 See also FDA 2001a; one of the arguments the FDA made in the proposed PBN rule was that a mandatory notification process was necessary to give the agency adequate knowledge about what products were being introduced into the marketplace.

23 Section 303 of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (PL 107-188) gives the FDA the power to temporarily detain a food article through administrative action if "an officer or qualified employee" of the FDA "has credible evidence or information indicating that such article presents a threat of serious adverse health consequences or death to humans or animals."

ity to address food safety questions is doubtful, particularly under its current regulations.[24] (The question of whether APHIS may have new authority under the Plant Protection Act (PPA; 7 USC § 7701 et seq.) to assess food safety issues is addressed in the following section.) In general, APHIS has not addressed food safety risks in its regulatory activities for GE plants, although it has excluded from the notification process plants with genetic material that encode substances that are likely to be toxic to nontarget organisms, that are intended for pharmaceutical use, or that derive from human viruses and diseases (7 CFR § 340.3(b)). APHIS requires field trial permits for these types of plants.

As noted previously, the FDA lacks authority to require the pre-market approval of substances in food that are not food additives. Whether the FDA may be able to use its food additive authority to address the adventitious presence of potentially harmful substances is considered in the following section. To date, the FDA has not indicated whether or how it intends to address these issues at the field trial stage. In its 2001 PBN *Federal Register* notice, however, the FDA encouraged developers of nonfood-use plants that might enter the food supply to participate in the mandatory notification process—but it was unclear at what stage such consultation would occur (FDA 2001a).

The EPA has authority to regulate substances produced by GE plants that are intended to be used as pesticides. In granting EUPs for field trials, the EPA has authority to take into account the potential of a pesticidal substance to become mixed into crops intended for use in food as part of its broad authority to ensure safety, including safety from exposure to pesticide residues in the diet. The EPA also clearly has power to establish tolerances for pesticide residues in food and feed, regardless of the source of those pesticides (21 USC § 346(a)). However, pharmaceutical and industrial substances that are not intended for use as pesticides would not be covered by the EPA's PIPs regulations. The EPA's authority to consider food safety risks for industrial substances is discussed in the following section.

The adequacy of the current regulatory system to protect the public health from issues relating to adventitious presence and ensure confidence in the regulatory system is a matter of opinion. A summary of the arguments on both sides is presented below; note that they do not necessarily represent the opinions of the authors.

Arguments that the Current System Is Flawed

Containment efforts are inadequate and will inevitably fail. Even if APHIS's containment requirements could theoretically *achieve zero gene flow, the agricultural production system is too complex to ensure no errors and 100% compliance. A number of instances have been reported where food (or crops intended for the food supply) has been mixed with*

24 As noted in the previous chapter, APHIS's current regulations are based on the old Federal Plant Pest Act (formerly 7 USC § 150aa et seq.), which authorized APHIS to act to prevent damage to plants and plant products. The FPPA contained no provisions on food safety or public health. It might be argued that if an unsafe nonfood substance were inadvertently mixed into a crop intended for food, thereby harming its economic value, such a substance would be considered a 'plant pest' under the Plant Protection Act (7 USC § 7701 et seq.) because it causes "damage" to a plant product. However, the language of the FPPA focused on physical damage and disease caused by insects, viruses, and diseases, and there is nothing in APHIS's administration of the law that would indicate that APHIS supports a broader construction.

unreviewed substances from GE plants.[25] *The StarLink episode showed how even relatively small amounts of food crops can become mixed at low levels throughout the food supply; it also illustrated the significant economic damage to the food industry that could be caused by low levels of unapproved genetic material in food, even in the absence of evident health effects.*[26] *StarLink also revealed the technical difficulty of removing low levels of unreviewed or unapproved substances from the food supply.*[27]

If some failures are to be expected, public health cannot be protected by relying upon the FDA's post-market authority. Instead, the FDA should review or approve GE crops at the field trial stage for food safety risks posed by adventitious presence, particularly GE crops that produce nonfood substances such as chemicals and pharmaceuticals. If the StarLink protein had caused adverse health effects, the public health impact could have been widespread. As the use of biotechnology to develop nonfood-use crops continues to grow, opportunities for mixing with the food supply will only increase, and responding after the fact will be inadequate. Thus it is important to conduct early safety assessments to ensure that only substances that are safe are permitted to be grown when there is a possibility they could become mixed with food.

An early assessment and approval process also makes it easier for the agencies to act when a food crop becomes mixed with an unreviewed substance but has not yet entered the food supply. If it had early information, the FDA could more easily make the case that the adventitious presence of a substance in a food crop posed a safety threat, and the agency could take timely action to prevent its movement into the food supply.[28]

Arguments that the Current System Is Adequate

APHIS's containment guidelines, combined with strong monitoring and enforcement, are sufficient to protect the food supply from low levels of unreviewed substances, and the FDA's post-market authority to remove unsafe foods from the market provides adequate

25 StarLink corn is the most prominent example (Taylor and Tick 2001). More recently, experimental GE corn modified to produce a pig vaccine was discovered by APHIS to be mixed in with soybeans headed for the food market. APHIS fined the producers for permit violations and blocked the soybeans from going to market (USDA 2002).

26 Some groups oppose the idea that nonfood-use substances, like pharmaceuticals and industrial chemicals, be permitted at any level in food, even if they are safe; one concern is that consumers will reject foods with low levels of such substances despite an assurance of safety from the FDA. For example, in 2003 the National Food Processors Association (NFPA) wrote: "The food industry must have a '100% protection standard' against *any* contamination of the food or feed supply. In the absence of demonstrated effective controls and procedures to ensure against such contamination, the NFPA continues to vigorously oppose the use of food or feed crops to produce [pharmaceuticals] or industrial compounds." (See also Treibwasser and Olson 2003.)

27 The presence of StarLink was still being reported in some corn shipments in December 2002 (Fabi 2002). As a legal matter, the authority to remove StarLink from the food supply was straightforward, since it constituted a pesticide food residue that had not been given a tolerance or exempted from a tolerance by the EPA and was therefore per se illegal under the FDCA (21 USC § 342(a)(2)(B)).

28 The FDA's new power to temporarily detain food articles through administrative action if there is credible evidence of "serious health consequences" under Section 303 of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (PL 107-188) may provide additional authority to move quickly in such a case, but these new authorities are untested.

authority to deal with any problems that might arise. Unless a developer has a respectable body of published studies to demonstrate the GRAS status of an unreviewed substance, the FDA should not have a difficult time challenging a GRAS determination. APHIS, even assuming it has no authority to address food safety issues, can enforce permit violations that might result in unwanted adventitious presence, and any "movement" of a regulated article outside of a permit would be a violation of the PPA that APHIS could address in a number of ways. It is unrealistic to expect zero adventitious presence, and, in any event, low levels of unapproved food crops in the food supply are unlikely to present a food safety risk.

CLARITY, TRANSPARENCY, AND PUBLIC PARTICIPATION

Other key characteristics of a credible regulatory system include clarity, transparency, and opportunities for public participation. As discussed in the previous chapter, the EPA's process for approving pesticide tolerances is fairly clear and transparent. In the case of PIPs, the EPA has published several rules for categorical exemptions that allow for notice and comment under informal rulemaking (see, e.g., EPA 1994).

The FDA's current voluntary consultation process for foods derived from GE crops provides for relatively less clarity, transparency, and public participation, since it fundamentally involves confidential discussions between the agency and product developers. Unless a developer publicly discloses the existence of an on-going consultation, the first public notice of it is the FDA's release of its "no further questions" letter and its summary of the developer's data, both of which occur at the conclusion of a successfully completed consultation (FDA 1997a). The data submitted to the FDA by the developer is subject to disclosure under FOIA, except for trade secrets and CBI (FDA 1997a). The current process provides no opportunity for public participation. While the FDA has published general guidance to indicate the kind of data it will rely upon and the factors it will take into consideration, each consultation is an informal, case-by-case discussion between the FDA and the company and is inaccessible to other interested parties. In its proposed PBN rule, the FDA proposed a number of process changes to provide additional transparency, but the rule has not become final (FDA 2001a).

Possible drawbacks to increased transparency and public participation do exist. The current promise of confidentiality may encourage companies to talk with the FDA about their products so that risk concerns can be considered and discussed early in the development process. A more open system could potentially create disincentives for early consultation if disclosure would put a company at a competitive disadvantage, and it could encourage companies to withhold information until late in the process or to not disclose it at all.

Approaches to Resolving the Issues and Concerns

The following are options for addressing the issues raised in the previous section, should policy makers decide that change is desirable. The options address providing the FDA with greater pre-market authority for GE foods; clarifying the responsibility for potential food safety risks stemming from the adventitious presence issue; and improving clarity, transparency, and opportunities for public participation.

OPTIONS FOR MANDATORY PRE-MARKET APPROVAL AUTHORITY FOR THE FDA

As discussed previously, a range of opinion exists concerning the adequacy of the FDA's current voluntary consultation process, particularly as applied to likely future food products of agricultural biotechnology. In the event it is deemed desirable to enhance the FDA's authority in this area, a number of options for change are discussed in this section, along with arguments for and against each option. (See also Table 3.2.)

Make Notification Mandatory (Proposed PBN Rule)

Under the current FDA procedure, developers of novel foods derived from GE crops are encouraged to notify and consult with the FDA prior to bringing a product to market, in order to give the agency the opportunity to raise any potential food safety concerns (FDA 1992 and 1997a). Making such notifications mandatory, rather than voluntary, could enhance food safety and increase the credibility of the regulatory system. The FDA proposed such a change in 2001 in its draft PBN rule, but the agency has not acted to finalize that rule (2001a).

The FDA justified the proposed PBN rule on the basis that it was important for the agency to be informed about new foods entering the market, particularly given the probability that future biotechnology products would pose more difficult safety issues (2001a). As a general rule, regulatory agencies have the authority to issue regulations that enable them to carry out the duties assigned to them by Congress.[29] It is not clear, however, what legal sanctions the FDA could apply against a developer who fails to comply with a pre-market notification requirement. Under existing law it is not illegal per se to go to market without giving notification, since developers are free to take a GRAS product to market without any prior FDA review. To be sure, there is a risk of enforcement, but the FDA would need to prove that the product contained substances that were not GRAS, not just that the developer failed to notify the agency. In its 1992 policy, the FDA determined that most substances added by genetic modification are presumptively GRAS. For GRAS substances, then, the FDA's PBN rule, even if implemented, would not be legally enforceable.[30]

Add an Affirmative Finding of Safety by the FDA

Under current procedures, the FDA concludes the voluntary consultation process by issuing the sponsor a letter in which the agency says that it has "no further questions" and that the manufacturer is responsible for the safety of the food product (FDA 1997a). One way to enhance the agency's regulatory oversight and improve public confidence in the safety of GE foods could be for the FDA instead to make an affirmative statement of the product's safety at the conclusion of the process.

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29 For example, FDCA § 701(a) authorizes the FDA to issue regulations for the "efficient enforcement of the act." The courts have construed this authority to extend to regulations that are "justified by the statutory scheme as a whole" (*National Confectioner's Association v. Califano,* 569 F.2d 690,693, citing *Toilet Goods Association v. Gardner,* 387 U.S. 158, 163 (1967)). Whether the FDA's proposed PBN rule would fall within the scope of this authority, however, is open to question.

30 The FDA's PBN proposal (2001a) also implied that certain types of modifications might not be entitled to the GRAS presumption laid out in the 1992 proposal. Such non-GRAS substances might be food additives, which of course must be affirmatively approved by the FDA before being marketed (21 USC § 348).

Table 3.2 Comparison of Policy Options for Mandatory Pre-Market Approval

	MANDATORY PRE-MARKET NOTIFICATION	AFFIRMATIVE STATEMENT OF SAFETY	UNAPPROVED PRODUCTS PER SE UNLAWFUL	PUBLIC PARTICIPATION	USES EXISTING AUTHORITY	LEGAL AUTHORITY
1992 FDA Policy (current)	No	No	No	No	Yes	Reasonably clear
Proposed PBN Rule (2001)	Yes	No	No	Yes	Yes	Uncertain
Affirmative Safety Statement	No	Yes	No	No	Yes	Reasonably clear
PBN plus Affirmative Safety Statement	Yes	Yes	No	Yes	Yes	Very uncertain
Food Additive Approach	Yes	Yes	Yes[a]	Yes	Yes	Reasonably clear if supported by rationale and scientific findings
Coordination Approach (with Affirmative Safety Statement)	Yes[b]	Yes	Yes[c]	Yes[d]	Yes	APHIS's authorities clear, but very uncertain how they apply to plants that pose only food safety questions
New Legal Authority	Yes	Yes	Yes	Yes	No	Clear if spelled out in legislation

a. Unless a court defers to the FDA's classification, the FDA would need to prove lack of GRAS status to establish an enforcement case that the unapproved product involves a food additive.

b. Under the Plant Protection Act.

c. Under the Plant Protection Act, but it is unclear if APHIS could use authority under the PPA solely for food safety concerns. Plants that are deregulated under the PPA would need first to be re-regulated under the PPA before APHIS could enforce.

d. Under the Plant Protection Act.

This could be done in several ways. The FDA could state in the letter, for example, that it agrees that the developer has an "adequate basis" for its conclusion that the product meets the applicable safety standards. This statement would affirm that the developer has conducted the appropriate tests and made appropriate judgments. While stronger than the current "no further questions" language, this formulation would not be a formal FDA approval. It does not express the FDA's own, independent opinion about the safety of the product, and does not bind the agency.

The FDA could go further and express its independent opinion on the safety of the product. A formal FDA finding of safety could provide a legal "safe harbor" for food companies

and others who may otherwise be exposed to liability and consumer concerns (Treibwasser and Olson 2003). The agency might be reluctant, however, to make such a finding without conducting a more thorough study than it does under the current voluntary notification and consultation process.[31] Though simple in concept, an administrative shift to an affirmative finding of safety approach would likely involve a significant change in the FDA's oversight of GE foods and in the interaction between the FDA and the developers of such foods. This change would flow from the fact that the FDA would be taking a share of the responsibility for the safety of GE foods, rather than relying as heavily as it does today on the developers' safety determinations. In taking on this responsibility, the FDA would likely have to: (1) provide more detailed guidance on the data required in a notification and require more data than is currently required or ordinarily submitted; (2) conduct a more in-depth review of the data; (3) verify the quality of the developer's data; and (4) make and document its own safety determination. This would in turn require additional staff resources and possible delays in product reviews.

Also, as with the pre-market notification requirement, the FDA has no legal authority to enforce a requirement that a developer receive an approval letter of any kind before going to market with a GRAS product. Thus, changing the language of the letter does not address the fundamentally voluntary nature of the review process. Again, while the FDA may not have legal authority, there would nevertheless be strong market pressures on companies to comply.

Finally, if an affirmative safety statement is combined with a mandatory requirement for a pre-market notification, legal questions arise. Put together, the two policies begin to look like a mandatory pre-market approval process for GRAS substances, something that Congress decided against in 1958 and the FDA has consistently said is not legally required.

Employ a Food Additive Approach

As noted previously, food additives are considered by the FDA under a mandatory pre-market approval process. Unless a food additive has been approved by the FDA as safe, food containing the additive is considered adulterated and cannot legally be marketed (21 USC § 348).

Some have suggested that all foods derived from GE crops should be regulated under the FDA's authority to approve food additives (*Alliance for Bio-Integrity, et al. v. Shalala*, 116 F.Supp.2d 166 (D.D.C. 2000)). Whether the FDA in 1992 could lawfully have adopted a regulatory approach in which it treated all or most of the substances added by genetic engineering as food additives remains an open issue. However, for the FDA *now* to adopt such a policy would require it to reverse some of the scientific findings it made in its 1992 policy statement and reaffirmed in its 2001 proposed rule.[32] While the FDA's previous poli-

31 An FDA finding of safety would also likely be a 'final agency action' within the meaning of the Administrative Procedure Act and thus would be subject to judicial review (5 USC § 704).

32 In 1992, the FDA indicated that most genetic modifications would result in added substances that were presumed to be GRAS. The DNA of the genetic construct is considered harmless, since the nucleic acids that compose DNA are ubiquitous in food. The FDA also stated that expression products, such as proteins, carbohydrates, fats, and oils, were also unlikely to present safety concerns if such substances were substantially similar to those already in food.

cy positions are not legally binding, it would need new information that justifies reversing its prior scientific determination in order to withstand judicial scrutiny under a 1983 decision of the Supreme Court (*Motor Vehicles Mfrs. Ass'n v. State Farm Mut. Aut. Ins. Co.*, 463 U.S. 29 (1983)). However, the agency might be able to use the rationale laid out in its 2001 proposed PBN rule—that future food products of genetic engineering are more likely to result in substances that could raise food additive questions—to reverse its prior *policy* position and provide additional guidance as to which products might presumptively be food additives. Whether a court would find that argument persuasive is open to question.

Even if the FDA could now lawfully classify substances added to foods via genetic engineering as food additives, that would not necessarily ensure that all such foods would be subject to a mandatory pre-market approval process, since the law permits developers to take GRAS foods to market without prior review. In an enforcement action, the FDA would need to challenge the marketer's assertion that the product is GRAS. While a court might be inclined to defer to the FDA's determination that such substances are presumptively food additives, such deference would depend on whether the FDA's regulation establishing the food additive presumption showed new evidence providing an adequate justification for the change in the agency's position, given the legal standard established in the *State Farm* case noted above.

The food additive process, moreover, has some significant disadvantages. Even for conventional food additives, the process has proven to be costly and time-consuming. The FDA has struggled to find ways to streamline it, with little success. The use of the food additive process for GE foods would very likely slow the introduction of new biotechnology products.[33] The FDA might be able to expedite consideration if it had additional resources.

The FDA might be able, also, to develop a special set of expedited procedures specifically for GE foods under the food additive rubric, much as it defined special procedures for the GRAS affirmation process. Under this option, traditional food additives would still need to go through the formal rulemaking process established in FDA practice, but GE food would move through procedures that could be streamlined and tailored to the safety issues likely to be raised by genetic modifications. In theory, this expedited process could reduce some of the concerns about the costs and delay associated with food additive proceedings. Again, however, there is some question about the legal justification for creating a separate food additive approval process for GE foods. In addition, any product approved as a food additive, regardless of the procedure, would be required to meet the standard of posing a "reasonable certainty of no harm" (21 USC § 346a(b)(2)(A)). This standard, as developed over the years in FDA practice, is a relatively high one, requiring significant data collection. As a result, there is a question whether any set of procedures would in practice allow a significantly faster or less burdensome process as long as the legal standard of "reason-

33 It has been estimated that developers spend an average of $20 million on research alone to support GRAS determinations for novel direct food additives (Noah and Merrill 1998, 375). The OSTP indicated in its proposal on the Coordinated Framework that the average food additive petition took between five and seven years (1984). The FDA's effort to introduce a GRAS affirmation petition as an alternative to a formal food additive petition was not an appreciable improvement; the average GRAS affirmation petition took more than seven years (Noah and Merrill 1998, 379). The FDA largely abandoned that effort in 1997.

able certainty of no harm" applied. For added substances that are currently considered GRAS, meeting the "reasonable certainty of no harm" standard may not be burdensome.

As an alternative, the FDA could maintain its present policy, which presumes that some added substances are likely to be GRAS, but it could define by guidelines more clearly what characteristics of future GE foods are likely to be treated as presumed food additives. In the 1992 policy statement and the 2001 proposed PBN rule, the FDA provided some general guidance as to the distinction between added substances that are likely to be GRAS and those that are likely to be food additives. Providing more specific guidance would help improve transparency and clarity while possibly bringing more future GE foods into the food additive process. To the extent that the FDA would characterize substances as presumed food additives that it had previously presumed to be GRAS, it would have to articulate a justification for reversing its past policy to overcome potential legal challenges. However, if the FDA were characterizing substances as food additives for the first time, courts would likely defer to the FDA's expert judgment.

Employ a Coordination Approach

To achieve the functional equivalent of a mandatory pre-market approval process, the FDA might be able to coordinate its current voluntary food safety consultation process with the USDA's mandatory review process under the Plant Protection Act. As noted previously and discussed in detail in Chapter 2, APHIS has authority under the PPA to review most GE plants (including food crops) for their potential adverse effects on crops and other environmental impacts. In general, GE plants cannot be commercialized unless APHIS determines either that the plant is not a plant pest (thereby deregulating it) or that it can be grown only under a permit.[34] Most commercial crops being grown today have been deregulated. Planting a GE crop without the appropriate APHIS approval is illegal; that is, APHIS has broad authority to take an unapproved crop from the market by showing in an enforcement action that a plant is a regulated article and that it lacks the required approval (7 USC § 7734).

In this option, then, APHIS and the FDA would coordinate their respective administrative processes. APHIS would withhold a permit or a deregulation decision for a GE crop until the agency was notified by the FDA that the FDA had satisfactorily completed its voluntary food safety consultation process. As a practical matter, without an APHIS permit or deregulation decision, a crop could not be commercialized; therefore the coordination between the two agencies would, in effect, create a mandatory pre-market approval process that would incorporate both food safety and environmental issues.

If APHIS's approval is merely an accommodation to the timing of findings by the FDA, APHIS could defer its own determination in the interests of comity until the FDA had the opportunity to review the product and determine that it had no further questions. However, while agencies have a good deal of latitude to develop procedures for administrative efficiency and convenience, it is questionable whether such a procedure could be used to achieve a substantive outcome that neither agency could achieve on its own. It is clear

34 As noted in the previous chapter, however, it may be possible under some circumstances to grow commercial quantities of GE crops under APHIS's notification provisions and without affirmative approval by APHIS.

from the prior discussion that the FDA itself has no authority to impose a mandatory pre-market approval process for GRAS substances. The question is therefore whether APHIS has independent authority to deny a permit on the basis of food safety concerns.

As noted in the previous chapter, APHIS's current permitting regulations are based on its authority to regulate plant pests under the repealed FPPA and, as stated previously, there is no language in that law that appears to give APHIS any authority over food safety or public health. However, the recently enacted Plant Protection Act could arguably provide APHIS with authority over food safety concerns. The definition of "noxious weed" in the PPA includes any plant that directly or indirectly injures or causes damage to "public health" (7 USC § 7702).[35] The question is whether this provision gives APHIS adequate legal authority to deny a permit for a GE crop solely on the basis of a food safety concern or take an unapproved crop off the market because of a food safety problem. There is nothing in the sparse legislative record to suggest that Congress intended to expand APHIS's traditional focus on plant health and crop protection to include food safety issues, which traditionally fall under the FDA's authority. Nor is there an indication that Congress intended to subject GRAS substances to pre-market regulatory review for food safety by APHIS. As a result, there is significant uncertainty about the scope of this authority in this particular context. As a matter of policy, APHIS is probably unlikely to assert such authority since food safety issues are well outside its traditional scope of expertise. In any event, APHIS has not indicated one way or another its intention with regard to implementing the noxious weed provisions of the PPA, although it has requested public comment on the issue (APHIS 2004).

An additional question exists regarding reliance on APHIS to enforce food safety concerns. Most GE crops that have been commercialized have been deregulated by APHIS, meaning that the agency has determined that they are not plant pests or potential plant pests and therefore are not under the authority of APHIS to regulate (7 CFR § 340.6). As discussed in the previous chapter, to re-regulate a crop that APHIS has deregulated would require APHIS to determine—presumably through new information—that its prior determination was no longer accurate and that the plant is, indeed, a plant pest. If a food safety concern arose with respect to a deregulated crop, it is not clear that APHIS would have the authority to take any action on that basis. APHIS could argue that the injury to "public health" would make the crop a potential noxious weed. However, the ambiguity over the scope of APHIS's public health jurisdiction leaves this issue uncertain as well.

Some also argue that casting APHIS in the role of the enforcer of the FDA's food safety standards is not only inappropriate, but would lack credibility, both because the procedure lacks clarity and because the public perceives that the FDA, not APHIS, has responsibility and expertise for ensuring food safety.

35 Harm to "public health" was included in the definition of 'noxious weed' in the earlier Federal Noxious Weed Act, enacted in 1974. Under the prior definition, APHIS has listed four noxious weeds in which it cited "public health" as at least one of the reasons for the listing: Giant hogweed in 1981, kodo millet and African boxthorn in 1983, and Cape tulips in 2000. Each of these weeds is toxic to both humans and livestock. Beyond these listings, there is no history of use of the "public health" rubric in the USDA's implementation of the plant quarantine statutes.

Provide New Legal Authority

The options discussed previously, which seek to help achieve the functional equivalent of a mandatory pre-market approval process at the FDA for future GE foods, all arguably fall within the FDA's existing legal authority. The FDA could adopt these interpretations without additional legislative authority, although its interpretations could be subsequently set aside in a court challenge, given the legal questions noted.

This final option, by contrast, considers providing the FDA with clear authority through new legislation. A legislative approach has several advantages. Since Congress could write the new law in any number of ways, a legislative fix could achieve any desired regulatory goal, including a mandatory pre-market approval process, greater transparency, and an opportunity for public participation to help build confidence in the regulatory system. Amending the law would allow the FDA to chart a course between the more onerous requirements of a food additive rulemaking and the GRAS process that technically allows developers to go to market without any prior FDA review. Such an approach would provide greater certainty for developers by making the regulatory pathway more clear. This approach could result in a process more tailored to GE foods and would make it easier to bring to market those biotechnology products that would otherwise be subject to a food additive proceeding.[36] It would provide a clear legal basis for FDA action and avoid the need for the FDA to reverse prior presumptions or make new scientific findings. By taking GE foods out of the GRAS/food additive framework, it also avoids creating potentially disruptive precedents for conventional foods and food ingredients. New authority could also address the issue of what legal standard of safety to apply, and require the FDA to make an affirmative finding of safety to provide a legal "safe harbor." New legislation would not necessarily be much slower than an administrative approach, given the lengthy time and effort required to implement some regulations.

A legislative approach also has several downsides, however. One is simply that, given the vagaries of the legislative process, the law that emerges from Congress may not contain the desired outcomes. Many groups with interests that go beyond GE food could use an effort to amend the FDCA as an opportunity to address their own issues. The fear that amending any part of the nation's basic food law could open a legislative Pandora's box is one reason that such major laws rarely get amended.

In addition, many are loathe to carve out a large exception to the nation's basic food law, which has been developed over nearly 100 years. New laws can create new uncertainties; the FDA would need to implement the new law with new regulations, which would take time to promulgate and would inevitably raise new issues. The uncertainty and time delays associated with a legislative approach could jeopardize the approval of products that are caught between the old system and the not-yet-implemented new system. In addition, changing the law, more than changing regulations, could be misread by export markets as

36 If desired, legislation could also adopt a novel foods approach that would subject all novel foods, whether developed via biotechnology or not, to pre-market review by the FDA. As the FDA and others have noted, the potential food safety risks posed by foods derived from GE plants are not different in kind from those posed by conventionally produced foods. For example, Canada employs a novel foods approach. However, this approach would greatly expand the number of products subject to FDA pre-market review, mark a clear change from the current statutory scheme, and likely generate significant debate.

an admission that the current process does not ensure product safety, which could provide additional fuel for trade disputes. Given all of the downsides of a legislative approach, and the general adequacy of the current system, some would argue that the improvements that could be achieved through legislation are not worth the risks.

If a legislative approach is deemed necessary and useful, it could take different forms and include different elements. An example of one approach is set out in Figure 3.2. However, other legislative approaches could be developed to achieve similar policy outcomes.

OPTIONS FOR PRE-MARKET REVIEW OF FOOD SAFETY RISKS POSED BY THE ADVENTITIOUS PRESENCE OF UNREVIEWED SUBSTANCES

As noted, neither the FDA nor APHIS appears to have clear responsibility for assessing potential food safety risks that might be posed by the inadvertent mixing of unreviewed GE crops, including nonfood-use crops, with crops intended for food or feed, *before* such crops are grown in field trials or commercially. APHIS regulates field trials to ensure that experimental crops are contained, and the FDA has the authority to respond to food safety problems that might arise after mixing has occurred. The EPA does have authority to consider food safety risks at the field trial stage for PIPs. In the event that the current regulatory approaches are deemed inadequate, the policy options that follow could be considered for addressing this issue.

Clarify FDA Policy

The FDA may have several means for reviewing potential safety concerns raised by the possible mixing of unreviewed substances, including nonfood substances, at the field trial stage. For example, the FDA could encourage developers to voluntarily consult with the agency at the time they submit notifications or permit requests to APHIS, thereby providing the FDA with basic safety information about any genetic material or expression products that could be transferred to food. This would give the FDA notice and information about field trials and provide the agency with an opportunity to raise concerns about substances that could pose a food safety issue.

The FDA could also plausibly employ its food additive authority. The agency could argue that, in a case in which containment is not possible and some level of adventitious presence is probable, the presence of a substance from an unreviewed GE crop in the food supply would constitute an indirect food additive under 21 USC § 348. The FDA could say that the presence of the substance in food is a reasonably foreseeable—and therefore intentional—consequence of planting the GE crop. If the substance was not generally recognized as safe, the FDA could arguably claim that the GE plant could not be grown until the developer had demonstrated in a food additive rulemaking that the material posed a reasonable certainty of no harm. A food additive approach would also enhance the FDA's ability to respond to a problem if the adventitious presence of a substance posed a safety issue—the agency would need only argue that the substance is an unapproved food additive under 21 USC § 348, instead of needing to prove under 21 USC § 342(a)(1) that it "may render" a food injurious. If, on the other hand, a substance were GRAS, the FDA would have no legal authority to require a pre-market review or approval process.

Figure 3.2 A Possible Legislative Approach

Purpose – To require that all food derived from genetically engineered (GE) plants be approved by the FDA prior to marketing, under legislative authority and procedures separate from those of Section 409 of the FDCA (21 USC § 348) and tailored specifically to ensure the safety of such foods on a scientific and expeditious basis.

Scope – The approval requirement could apply to:

- GE foods intended for human consumption;
- GE feeds intended for animal consumption; and
- any transgenic product of a GE plant that could be consumed by humans or animals.

Definitions – 'GE plants' could be defined as plants that are developed using a transformation event that involves the introduction into the plant of genetic material that has been manipulated in vitro. 'GE foods and feeds' could be defined as foods and feeds derived from such plants.

Approval Requirement – It could be made unlawful to offer for sale any product that is subject to this provision, or to use a GE crop that could be consumed by humans or animals for the commercial production of a nonfood substance, unless the food or crop has been licensed under this provision.

Approval Application – To obtain a license, a person would submit to the FDA an application containing the following information:

- A description of the food product or plant, its intended use, and the nature of the genetic modification used to produce the food or plant
- A description of any new substance added to the food, as well as intended or unintended compositional changes in the food or plant resulting from the genetic modification compared to a traditional counterpart
- Data demonstrating the safety of any new substance added to the food and that there is no compositional difference between the GE food or plant and its traditional counterpart that raises a safety question requiring testing or analysis beyond the compositional comparison, or data and analysis demonstrating that, despite such compositional change, the food or plant is safe for consumption by humans, animals, or both, as appropriate
- A statement by the applicant that it considers the safety of the food or plant to be demonstrated on the basis of compositional comparison alone (Category I) or that additional testing or analysis is required to demonstrate safety (Category II)

Approval Standards – A GE food or plant could then be deemed safe and a license could be granted if the FDA finds that:

- in the case of a Category I food or plant, the GE food or plant is as safe as the traditional counterpart; or
- in the case of a Category II food or plant, the compositional comparison and the additional test data and analysis in the application demonstrate that the GE food or plant poses no safety concern under its intended and reasonably anticipated conditions of use.

Application Review and Approval Process – Following the submission of an application, the FDA would do the following:

- Within 60 days, conduct a preliminary review and (1) notify the applicant that the application is complete and ready for substantive review or inform the applicant of the data required to make the application complete, and (2) in the case of a complete application, inform the applicant whether the food or plant will be reviewed as a Category I or Category II food or plant
- Within 90 days of the submission of a complete application, publish a notice that the application has been accepted for substantive review and place the application on public display, as provided in the disclosure of information section below

Figure 3.2 A Possible Legislative Approach (...continued)

- In the case of a Category I food or plant, within 180 days of the submission of a complete application, grant a license or inform the applicant that the application is not approvable and the basis for that determination
- In the case of a Category II food or plant, within 270 days of the submission of a complete application, grant a license or inform the applicant that the application is not approvable and the basis for that determination

Conditions of Approval – In granting a license, the FDA could impose such conditions on the production and use of the food or plant as the agency determines are necessary to ensure the safety of the GE food or plant, and such conditions would be incorporated in and become terms of the license.

Advisory Committee – If an application raises significant or unusual safety questions, the FDA could in its discretion present such questions to an expert advisory committee for review and comment. In such cases, the FDA could extend the time for action on the application for up to 90 days or such additional time as may be agreed to by the applicant.

Pre-Submission Consultation – Prior to the submission of an application, the FDA could, upon the request of a potential applicant, consult with the applicant on the information and data required to be submitted in the application or on other matters that may affect the outcome of the review or its timely completion. The fact of such consultation would not be protected from disclosure unless the potential applicant demonstrates in advance of the consultation that the fact that the product is under development is confidential business information. The data and information submitted to the FDA in conjunction with the pre-market consultation would not be disclosed.

Disclosure of Information – When a completed application is placed on public display, all information contained in the application would be disclosed, except to the extent the applicant demonstrates in advance that the information involves trade secret manufacturing methods or processes.

Public Participation – Any person could, within 30 days of the notice of acceptance of an application, submit comments or other relevant information concerning the application to the FDA. The FDA would consider such information in acting on the application.

Fees – The FDA could be authorized and directed to establish a fee schedule and collect from applicants fees sufficient to cover the cost of the license program.

Judicial Review – The granting of a license for a GE food or plant would be subject to judicial review in the U.S. Circuit Court for the District of Columbia Circuit, should any person wish to file a complaint.

Regulations – To implement the pre-market approval process, the FDA would, within one year of enactment, issue regulations or guidance, as appropriate:

- establishing criteria for what constitutes a traditional counterpart to a GE food or plant;
- establishing criteria for making the compositional comparison between the traditional counterpart and the GE food or plant, including the required nature and intensity of the compositional analysis of the GE food or plant;
- establishing criteria for deciding when a compositional difference raises a safety question that justifies shifting a GE food or plant from Category I to Category II (including the nature and extent of the intended compositional change, the nature and extent of unintended changes, and the change in levels of constituents present in the traditional counterpart(s));
- providing guidance on the data and analysis required for a Category II food or plant;
- defining the process for review of applications, including disclosure of information and public participation; and
- establishing a fee schedule.

Alternatively, it is possible that the FDA could use its existing authority to issue guidance that would establish action levels to address unintended "contamination" under 21 USC § 342(a)(1), much as it currently does for unavoidable environmental contaminants such as mercury in fish (FDA 2000). Guidance would provide consumers with some assurance that the adventitious presence of some substance does not pose a food safety risk, and would provide the industry with an understanding of what levels of adventitious presence could trigger a post-market enforcement action under 21 USC § 342(a)(1) or (2). Implementing this option would require the FDA to invest resources to develop data and issue guidance. To date, however, the FDA has not indicated whether it intends to use this or any other approach to address at the pre-market stage any potential food safety issues that might be posed by the inadvertent presence of nonfood-use genetic substances in food crops.

The advantage of using existing food safety authority to deal with adventitious presence is that the FDA could more quickly provide assurance that the food supply would be protected in the event that food crops became mixed with nonfood or unreviewed substances. The agency could also fairly easily establish responsibilities for developers, growers, processors, and marketers. This option gives the FDA a tool to address the substances produced by GE plants that are most likely to raise food safety issues in the event they become mixed with the food supply. Such approaches, however, would require the agency to invest additional resources in safety assessments at the field trial stage, which could be a significant challenge. In contrast to the 50 or so consultations that the FDA has conducted in the last 10 years, nearly 8,000 field trials have been conducted (according to APHIS's database)—although the number of transformation events involved is likely to be much smaller. While only a fraction of these likely would have raised food safety concerns, it is unclear how the FDA would manage the reviews of field trials as a practical matter.

The use of existing authority has some additional drawbacks. The FDA's powers under the food additive provisions may have only limited application, particularly where unreviewed substances are likely to be GRAS. The FDA would have no authority to require GRAS substances to be assessed for risk prior to field trials. Further, the FDA's regulatory authority in this area is not completely free of doubt, since it would require the agency to assume that the accidental mixing of nonfood genetic material into food crops was nevertheless a reasonably foreseeable consequence to constitute being a substance intentionally added to food.

A possible effect of an FDA review could be to permit "safe" levels of genetic materials from unapproved GE crops into the food supply. Some in the food industry oppose the concept of permitting any tolerance level for nonfood substances in food crops, regardless of safety (NFPA 2003). As a result, they may not support such a regulatory structure.

Revise the EPA's EUP Exemption for Small-Scale Field Tests

The EPA regulates experimental field trials greater than 10 acres for PIPs. Developers conducting smaller-scale field tests are not required to notify or get approval from the EPA as long as food or feed crops are destroyed or the PIP has a pesticide residue tolerance or an exemption. As noted in the previous chapter, one option would be for the EPA to revise this exemption so that even small-scale field tests of PIPs would have to obtain prior EPA approval, so that the EPA could impose any appropriate conditions needed to minimize the possibility of mixing with food crops. However, the EPA's authority under FIFRA extends only to GE crops that produce pesticidal substances. Alternatively, if APHIS oversight were

deemed sufficient, the EPA could consider relaxing its EUP restrictions, or APHIS and the EPA could consider harmonizing elements of their field trial oversight.

Use FDA, EPA, and USDA Authorities under Nonfood Laws

It may be possible to address the issue of adventitious presence using nonfood laws. For example, the FDA has broad authority under separate provisions of the FDCA to approve human and animal drugs.[37] Under this authority, the manufacturer of a new human or animal drug cannot market it without the FDA's prior approval that the drug is both safe and effective for use when used as directed. The FDA also has broad authority to regulate the manufacture and production of human and animal drug products to ensure quality and consistency (FDCA § 501 et seq.; 21 USC § 351 et seq.).

Under these provisions, the FDA clearly has authority over the chemicals harvested from GE crops that are produced for human or animal drug use. As part of its authority to regulate the manufacture and production of human drugs, the FDA could issue good manufacturing practices (GMPs) for pharmaceutical chemicals made by GE plants, much as it has for more conventional production facilities (21 USC § 210.1). Since the purpose of the FDCA is to ensure that drugs are "safe," the FDA could arguably interpret *safe* broadly to ensure that the drug production process does not pose a risk to humans through inadvertent mixing in the food supply. Under that interpretation, those GMPs could therefore include guidelines for the containment of PMPs or other measures to prevent PMPs from becoming mixed with the food supply. Legal questions exist, however, about how far the FDA can go in addressing the field trial stage of product development for PMPs; in particular, field trials carried out for research purposes by a developer before an investigational new drug application is submitted may not be covered by the FDA.

The FDA issued a guidance document on pharmaceutical plants in October 2002 that suggests it is prepared to use its authority under Section 501 (21 USC § 351) to regulate the production of pharmaceuticals in plants, but how far the agency would go in setting and enforcing containment standards for pharmaceutical plants remains to be seen (2002a). To date, the FDA has deferred to APHIS's guidelines and permit requirements for the containment of nonfood-use plants; the guidance document suggests only that developers of pharmaceutical plants consult with the FDA's CFSAN if there are possible food safety concerns about inadvertent mixing.

The FDA's authority under the human and animal drug approval provisions of the FDCA would extend only to plant-made substances intended for use as human or animal drugs. For any other nonfood use, such as industrial substances, the FDA would need to rely upon its general authority under the food safety provisions of the FDCA.

The EPA may have jurisdiction over some of the industrial substances produced by plants, provided that they fall under the definition of "new chemical substances" under the Toxic Substances Control Act (TSCA; 15 USC § 2601 et seq.). As discussed in Chapter 2, TSCA requires pre-manufacturing notifications for new chemical substances and for significant new uses of existing chemical substances. Whether the production of existing chemicals in a new manner (i.e., by plants) would constitute a significant new use is one of a number

37 USDA's Center for Animal Biologics has jurisdiction over new animal biologics, such as vaccines.

of questions that would need to be examined to determine TSCA's authority over PMIPs. In theory, however, the EPA might be able to fashion a rule, similar to the PIPs rule under the pesticide program, under which the agency could review the potential environmental and health impacts of PMIPs, including the potential for adventitious presence in the food supply. How far the EPA could go in regulating the production of chemicals in the field in the case of nonfood-use crops is an open question.

The advantage of using existing, nonfood safety laws is that it enables agencies to use their authorities to reach many of the substances that may be grown in plants, to provide assurance that the food supply is safe. However, this option would require agencies to interpret their authorities broadly to cover growing crops as a manufacturing process. In some cases, the application of rules that make sense in the context of industrial or pharmaceutical production facilities will make little sense when applied to farms. Agencies that lack experience dealing directly with growers may find it difficult to bridge that gap.

Give the FDA New Authority to Conduct a Pre-Field Trial or Pre-Market Review

While the FDA may have authority under existing laws to address some of the potential food safety risks that could be posed by the inadvertent mixing of unreviewed and nonfood substances with food crops, its authority is limited by the need to address them in the context of the food additive/GRAS authorities of the FDCA, which could limit its premarket authority. If additional authority is needed, legislation could be drafted that would clarify or expand the FDA's authority. Congress could give the FDA explicit authority to assess the food safety risks of all food crops, regardless of whether or not they are grown for food purposes. This authority would give the agency clear responsibility for ensuring the safety of the food supply from crops being produced for nonfood-use purposes, without resorting to a food additive process. As noted previously, legislation could be drafted to achieve such an outcome. However, the legislative process is not predictable and the results may not achieve the desired goals. Moreover, legislation can create new legal uncertainties and delays as agencies develop rules to implement the new law.

OPTIONS FOR GREATER CLARITY, TRANSPARENCY, AND PUBLIC PARTICIPATION

Options for improving the clarity and transparency of the FDA review of GE crops were identified by the FDA itself in its PBN rule (2001a). To make the consultation process more open and clear, the FDA could provide notice of the existence of an on-going consultation and make available a summary of the data provided by the developer before a consultation is completed. The FDA could also simply place the data that could be obtained under FOIA on the internet, thereby reducing transaction costs for requesters and the agency.

To date, the FDA has not proposed allowing public comment on consultations. In part, this is probably because consultation is a voluntary process that has no formal legal effect, and, as a result, there is no clear justification for a public comment component. At the same time, the FDA has acknowledged the public interest in the consultation process (2001a), and a public comment opportunity could help alert the agency to any issues that it should be considering and could help to ensure transparency and credibility.

As noted in the PBN proposal (FDA 2001a), the FDA has authority under existing laws to enact procedures to enable public participation and greater transparency of its regulatory

oversight process. Its ability to provide greater disclosure of information submitted by developers is limited by criminal prohibitions against the disclosure of CBI, but the agency may be able to more aggressively challenge companies' claims of what constitutes CBI in order to provide greater public disclosure. The FDA has already adopted a general policy requiring the disclosure of safety data (21 CFR § 20.111).

Regulating Genetically Engineered Animals

Numerous genetically engineered (GE) animals and products derived from those animals are currently under development in laboratories around the United States (NRC 2002a and 2004).[1] Only one, a transgenic ornamental aquarium fish, has been commercialized (Weiss 2003); no other GE animals nor products derived from them have yet been marketed. The first GE food animal to be commercialized may be a type of salmon that contains an introduced growth hormone (Martin 2003). Other GE animals under development include animals that:

- produce pharmaceuticals for animal or human use,
- contain other substances that can be processed into commercial products,
- are disease-resistant or have other desirable production attributes, or
- contain organs or tissues that can be transplanted into humans.

Some of these animals may be intended to enter the food supply (e.g., the faster-growing salmon), while others are intended for nonfood uses and may need to be kept out of the food supply (e.g., cows that produce human drugs in their milk).

No new laws have been codified to specifically address the regulation of GE animals. And, because GE animals are so new and are still largely being used only in research, the agencies likely to oversee them have not yet established clear overall or product-specific policies for regulating them under existing laws. Regulators, researchers, developers, and potential consumers are thus currently navigating in uncertain waters, and the discussion of regulatory policies in this chapter is necessarily somewhat speculative.

The Food and Drug Administration (FDA) may regulate GE animals under the new animal drug provisions of the federal Food, Drug, and Cosmetic Act (FDCA; 21 USC § 360b; CEQ and OSTP 2001). Nonetheless, it remains unclear exactly how this law would be applied to GE animals, and it is possible that other agencies, with other statutory authorities, may also play a role.

This chapter provides an analysis of the regulatory and policy issues regarding GE animals. The chapter contains four main sections. The first is an overview of some of the key issues under debate regarding GE animals. The second section describes the FDA's regulatory systems for new animal drugs and food safety and explains how these could apply to

1 In this report, the terms "GE animals" and "transgenic animals" are used synonymously to refer to animals whose genetic code has been altered as a result of human intervention through the addition of integrated exogenous DNA or the deletion of endogenous DNA, as well as offspring that inherit the genetic alteration. The Food and Drug Administration's Center for Veterinary Medicine defines the term GE animals more broadly to include all animals that have been altered by molecular biology techniques, including those whose changes are heritable (e.g., transgenic animals) and those whose changes are non-heritable (e.g., animals treated with gene therapy).

GE animals. The section also describes the animal and plant quarantine, animal welfare, and meat safety regulatory systems of the U.S. Department of Agriculture (USDA) and the potential roles each may play in creating a regulatory framework for GE animals. The third section describes in detail the key issues and concerns regarding the regulatory system for GE animals. And the fourth section outlines possible approaches—both administrative and legislative—for addressing those issues and concerns, should policy makers determine that change is needed.[2]

Overview of Key Issues

A recent report by the National Academy of Sciences' National Research Council (NRC) outlined in detail the potential food and environmental safety concerns relating to GE animals (2002a). (See Figure 4.1.) Some of these concerns are similar to those regarding GE plants. For example, the genetic modification of animals can raise potential food safety issues because such modification can both introduce novel proteins into food and cause other compositional changes to food. Also, GE animals—particularly fish and insects—have the ability to move about freely in the environment, reproduce, and potentially cross-breed with wild populations of their species, with possible detrimental effects on the wild species and the ecosystems in which they live. An issue unique to animals is concern about animal welfare; genetic engineering can alter animals in ways that could adversely affect their health and well-being. Given that the genetic engineering of animals remains mostly in the research stage, many of these concerns remain theoretical. Actual risks have not been quantified, although the NRC report indicated that many risks are expected to be generally low (2002a).

A key challenge for the commercialization of some GE animal species will be to ensure adequate containment, whether physical or biological, to prevent the escape of such animals into the environment or to successfully mitigate the risk of escape (NRC 2004). Also, policies and procedures will need to be developed, possibly including identification and tracking systems, to keep those GE animals and their progeny out of the food supply that are either not intended for or not yet approved for consumption as food. Effective regulatory strategies will be needed to ensure the health of GE animals and, in some instances, the safety of products and their use, as well as to maintain public confidence in the emerging uses of biotechnology and the associated federal and state regulatory systems.

The primary question in play is whether regulatory agencies, either individually or acting together, have sufficient authority under existing laws to establish a regulatory scheme to address all of these issues (NRC 2002a, 114). In 2001, case studies published by the White House's Council on Environmental Quality (CEQ) and Office of Science and Technology Policy (OSTP) suggested that the genetic engineering of animals could be regulated under existing legal provisions of the FDCA that govern "new animal drugs" (21 USC § 360b).

2 Note that genetically engineered insects are not discussed in this chapter. GE insects that are *plant pests* are covered by regulations under 7 CFR Part 340 pertaining to organisms modified through genetic engineering that are or may be plant pests. These regulations are administered by the USDA's Animal and Plant Health Inspection Service and are discussed in Chapter 2. For a more detailed analysis of regulatory issues associated with GE insects, see *Bugs in the System? Issues in the Science and Regulation of Genetically Modified Insects* (PIFB 2004).

Figure 4.1 Summary of the National Research Council Report

Animal Biotechnology: Science-Based Concerns

In 2002, the National Research Council's Committee on Defining Science-Based Concerns Associated with Products of Animal Biotechnology issued a final report. The committee sought to identify risk issues concerning the products of animal biotechnology; they were not asked to identify benefits. The committee's report noted that GE animals present unique challenges to science and public policy, because the products of such animals can be used for food and medical applications, animals are mobile, and animals are considered sentient organisms and the public has greater concern for their welfare than they do for that of plants (1-2). The report went on to detail risks and concerns associated with GE animals and animal products, including the following. (Page numbers are noted in parentheses.)

- "The committee considered environmental issues to be the greatest science-based concerns associated with animal biotechnology…in large part due to the uncertainty inherent in identifying environmental problems early on and the difficulty of remediation once a problem has been identified…. The release or escape of [GE] animals could result in a transgene spreading through reproduction with wild type individuals of the same species…. The [GE] organism eventually might replace its relative or become established in that community if it is more fit than its wild relatives in that environment" (9). "One case of immediate concern is the release of [GE] fish and shellfish" (11).
- "The genetic engineering of animals intended for use as food will involve the expression of new proteins in animals; hence the safety, including the potential allergenicity, of the newly introduced proteins might be a concern" (7). In general the committee concluded, however, that these products posed "moderate to low" food safety concerns (8).
- "Although animals engineered to produce useful products [other than food] will not be intended for consumption by humans or other animals, there are grounds for concern that adequate controls be in place to ensure restriction on the use of carcasses from such animals" (6-7).
- "The effects of genetic manipulation on animal health and welfare are of significant public concern" (11). "Some of the techniques in use are extremely inefficient in the production of [GE] animals. Efficiencies of production range from 0 to 4 percent in pigs, cattle, sheep, and goats, with about 80 to 90 percent of the mortality occurring during early development. Of the [GE] animals that survive, many do not express the inserted gene properly, often resulting in anatomical, physiologic, or behavioral abnormalities" (12).

The final chapter of the report addresses concerns related to scientific uncertainty, the policy context, institutional capacity, and social implications. In particular, the report noted the following.

- "The multiplicity of agencies and statutes potentially involved in regulating the safety and environmental aspects of animal biotechnology is a concern for scientists and other stakeholders, who will be seeking clarity about the scientific standards, data requirements, and analytical approaches to be applied in making market entry decisions. Without this clarity, it will not be possible to gather the necessary data with efficiency, and with confidence that the data will be scientifically sufficient and meet the government's regulatory needs.

Figure 4.1 Summary of the National Research Council Report *Animal Biotechnology: Science-Based Concerns* **(...continued)**

Moreover, without clarity concerning scientific requirements and the allocation of responsibilities among the federal agencies, the public will have difficulty understanding, evaluating, and ultimately, gaining confidence in the government's decisions" (114).

- "The [FDCA] is not...an environmental statute. It is thus unclear whether the "health of man or animal" language in the [FDCA's] definition of the safety standard for animal drugs will be broad enough to sustain FDA's regulatory authority over broad, systemic effects of animal biotechnology on ecosystems.... Nor is the CVM an environmental agency by mandate or tradition. Moreover, the agency lacks expertise in specialized areas that are relevant to assessing the environmental impacts of animal biotechnology, such as marine ecology and evolutionary biology" (114).
- "The committee's concern about legal and technical capacity is not limited to the CVM. It is not clear...whether any of the agencies with a possible regulatory role...has a clear and adequate mandate and the necessary scientific and technical expertise to address" the environmental impacts of animal biotechnology (115).

The case studies viewed inserted genetic constructs and their expression products as "drugs" because—consistent with the definition of "drug" in the law—they are intended to "alter the structure or function" of animals (CEQ and OSTP 2001; 21 USC § 321(g)(1)(C)). If the new animal drug approach is fully implemented, it would involve a rigorous review of the nature of genetic modifications and assessments of both food safety and target animal safety. Also, neither GE animals nor their products could be marketed lawfully nor enter the food chain without pre-market approval from the FDA.

On one level, the use of the new animal drug rubric appears logical, since genetic engineering clearly is intended to "alter the structure or function" of animals. Some observers, however, including the NRC (2002a), believe that the fit between the new animal drug approval provisions and genetic engineering is imperfect, in part because such engineering results in permanent genetic alterations that are inheritable. For example, it is unclear how the progeny of GE animals would be regulated under the FDCA's new animal drug rubric, since it is unlikely that the first animal created in a lineage of GE animals (sometimes referred to as the founder), would actually be the commercialized animal.

Also, the FDA may have only limited authority to consider potential environmental risks relating to GE animals. The FDCA does not explicitly authorize the FDA to consider environmental risks, nor does it contain a clear standard for making decisions regarding such risks. As a result, it is unclear whether the agency could deny an approval for a GE animal based on environmental concerns alone.

Another issue is the relative lack of transparency and opportunities for public participation in the new animal drug approval process. The FDA by law cannot reveal any information about interactions between the agency and new drug sponsors, through sponsors may make such information public if they wish (21 CFR § 514.12).

As an alternative to using the new animal drug approval provisions of the FDCA, the FDA could seek to assess only the food safety of GE animals entering the food supply, under the

agency's general food safety authorities (21 USC § 341 et seq.). To the extent that such a regulatory approach would operate much like the FDA's current policies for foods derived from GE plants (FDA 1992 and 1997a), many of the issues discussed in Chapter 3 would likely apply.

Laws administered by the USDA might also be used to regulate GE animals. The USDA's Animal and Plant Health Inspection Service (APHIS) administers laws intended to protect the health of livestock from communicable diseases,[3] ensure the humane treatment of research animals,[4] protect plants from pests that cause disease and injury,[5] and protect livestock from injurious wildlife.[6] The USDA's Food Safety and Inspection Service (FSIS) also plays a critical role in food safety by inspecting meat before slaughter.[7] The USDA has issued no guidance (other than for insects that are "plant pests" (7 CFR Part 340)) as to how, if at all, any of these authorities will be applied to the regulation of GE animals.

In theory the Animal Health Protection Act (AHPA; 7 USC § 8301 et seq.), which is intended to protect the health of livestock, might provide APHIS with authority to regulate the "environmental release" of GE livestock, similar to how APHIS uses its plant pest authorities to assess and regulate the movement of GE plants into the environment. Under the AHPA, APHIS might have clearer regulatory authority over some environmental concerns related to GE livestock and provide greater transparency and opportunity for public participation than appears to be permitted under the new animal drug provisions of the FDCA. In addition, APHIS has a long history of identifying, tracking, and quarantining animals that pose pest or disease risks to the livestock industry (APHIS 2002a). Such technical expertise and infrastructure could be valuable to the oversight of GE animal researchers, developers, and ranchers.

The application of the AHPA to the regulation of GE animals has some obvious weaknesses, however. The AHPA may not provide APHIS with clear authority over all animals of interest; on its face, the law applies only to modifications that raise livestock disease or pest concerns, which could be a small subset of GE animals. Furthermore, it is not clear how the AHPA would apply to the progeny of GE animals or to animals other than livestock. Finally, the law does not appear to provide APHIS with clear authority to consider the full range of environmental risks posed by GE animals.

Two other laws administered by APHIS could, in theory, have some application to GE animals. The Plant Protection Act (PPA; 7 USC § 7701 et seq.), discussed extensively in Chapter 2, applies to animals that are or could be plant pests, which could include grazing livestock. Recent amendments to the Animal Damage Control Act (ADCA; 7 USC § 426) could also, in theory, allow APHIS to regulate "injurious animal species." The scope of these laws as applied to GE animals is very unclear, however.

If policy makers decide that change is needed to address some of the concerns regarding the regulation of GE animals, they could take one or more of several possible approaches.

3 The Animal Health Protection Act (7 USC § 8301 et seq.)

4 The Animal Welfare Act (7 USC § 2131 et seq.)

5 The Plant Protection Act (7 USC § 7701 et seq.)

6 The Animal Damage Control Act (7 USC § 426)

7 The Meat Inspection Act (21 USC § 601 et seq.) and Poultry Products Inspection Act (21 USC § 451 et seq.)

For example, the FDA could undertake a number of administrative reforms—such as developing guidances specific to GE animals—to clarify the application of the new animal drug approval process to such animals. The FDA could also be given more explicit authority through legislative changes that could clarify the agency's environmental review authorities and improve transparency and public participation in the regulatory review process. Alternatively, the FDA could seek to apply only its food safety authority to those GE animals entering the food supply, and not address animal safety or environmental issues. On the USDA side, APHIS could set up a program under the AHPA to regulate some GE livestock in a manner similar to how it regulates GE plants under the PPA. Congress could also choose to make targeted legislative fixes to clarify APHIS's authority over potential environmental and other risks associated with GE animals.

Given the uncertainty about the regulatory approach that will be adopted, the FDA and the USDA will likely need to coordinate their authorities to determine appropriate roles and responsibilities.

The Existing Regulatory System

This section begins with a description of the FDA's existing regulatory systems, and then explores how those systems could be applied to GE animals. The section then describes laws enforced by the USDA and how they could also potentially be used to regulate GE animals. Table 4.1 summarizes the various FDA and USDA authorities that could potentially be used to regulate GE animals.

THE FDA

Two regulatory approaches used by the FDA are discussed here: the agency's new animal drug approval process and its food safety authority. Both of these approaches derive from the FDA's authorities under the Food, Drug, and Cosmetic Act (21 USC § 301).

The New Animal Drug Approval Process

The FDCA defines a "drug" in part as "any article" intended "to affect the *structure or function* of the body of man or animal" (emphasis added; FDCA § 201(g)(1)(c); 21 USC § 321(g)(1)(C)). Unless a drug to be used on an animal is "generally recognized as safe and effective" (GRASE), the drug constitutes a "new animal drug" under the law (FDCA § 201(v); 21 USC § 321(v)).[8] It is expressly unlawful to market a new animal drug without first submitting a "new animal drug application" (NADA) to the FDA and securing the agency's approval of the application. The consequences for violating this pre-approval requirement include the physical seizure of the new drug and related material and any food containing the new drug or its residues; the enjoining of responsible individuals from marketing the drug; and, in rare cases, the criminal prosecution of the offending parties

8 The word "new" does not necessarily connote novelty. Rather, it is a statutory term of art used to designate substances that are not "generally recognized" as both "safe" and "effective" for their intended use, or, if so recognized, have not been used to a "material extent or a material time" for such intended use. "General recognition" is also a term of art. Such recognition is determined on the basis of qualified expert opinion and publicly available scientific evidence (21 USC § 321(v)).

Table 4.1 Potential Regulatory Authorities for GE Animals

AGENCY	LEGAL AUTHORITY	SCOPE OF GE ANIMALS COVERED	PRE-MARKET APPROVAL	RISKS CONSIDERED
FDA	General food safety authority under the Food , Drug, and Cosmetic Act (FDCA)	Only those entering the food or feed supplies	No, unless food additive	Food safety
FDA	New animal drug approval authority under the FDCA	All	Yes	Food safety; animal safety; effectiveness; indirect human or animal health impacts
APHIS	The Animal Health Protection Act	Livestock only; scope uncertain, but probably very limited	Yes	Animal health; other environmental issues uncertain
APHIS	The Animal Welfare Act	Research animals only	N/A	Animal welfare
APHIS	The Plant Protection Act	Potentially broad	Yes	Injury to plants; limited for environmental risks
APHIS	The Animal Damage Control Act	Limited	No	Injury to agriculture and other interests

(FDCA § 501(a)(5); 21 USC §§ 351(a)(5) and 301-305). The new animal drug approval process is administered by the FDA's Center for Veterinary Medicine (CVM).

This section looks at several key elements of new animal drug regulation, including: standards for demonstrating safety and effectiveness; the investigational new animal drug exemption; NADA submission, review, and approval; post-approval controls; environmental assessment; and the labeling of animal drugs.

Standards for Demonstrating Safety and Effectiveness

Section 512(d)(1) of the FDCA (21 USC § 360b(d)(1)) requires that the safety of a new animal drug be demonstrated by "adequate tests by all methods reasonably applicable to show whether or not...[the] drug is safe for use under the conditions prescribed, recommended, or suggested" in the proposed labeling of the product. Safety in this context refers not only to the health of the target animal,[9] but also, in the case of a drug for use in food-producing animals, the health of humans who may consume the edible portions of the animals (FDCA § 201(u); 21 USC § 321 (u)).

9 In demonstrating animal safety, tests must delineate the potential "cumulative" effect(s) of the drug on the animal (FDCA § 512(d)(2); 21 USC § 360b(d)(2)). The FDA has traditionally interpreted this requirement as authorizing it to require the NADA sponsor to submit dispositive information concerning how much of a given drug an animal can safely consume, evidence of the potential reproductive effects that exposure to the drug may impart, and evidence documenting that the drug will not have a harmful impact on a specific component of the animal population (the young, the old, etc.) (CVM 1992; 21 CFR § 514.50(d)).

For a drug intended for food-producing animals, the FDA must evaluate a variety of issues concerning human food safety and target animal safety. To facilitate this evaluation, the FDA generally requires that the toxicological profile of the drug and its residues be established via the use of appropriate tests, including genotoxicity tests, short-term feeding studies, tests to evaluate the drug's effect on reproductive function and teratology (ability to induce birth defects), and, if appropriate, antibiotic-resistance tests. Because most drugs are metabolized, human food safety testing routinely focuses on metabolic pathways in the target animal, metabolic inactivation by the target animal, and the potential effects of the metabolites when consumed by people. The agency's ultimate food safety determinations derive from an assessment of the risks presented by the level of drug residue or its metabolite(s) in edible tissue (CVM 1994).

The FDCA also requires drug developers to submit scientific information demonstrating the effectiveness of the drug, including at least one investigation under actual field conditions of use. This information must amount to "substantial evidence" that the drug will have its intended effect in the targeted animal (FDCA § 512(d)(3); 21 USC § 360b(d)(3)).

The Investigational New Animal Drug (INAD) Exemption

A new animal drug intended solely for experimental and research use may be exempted from the general prohibition against the unlawful introduction of an unapproved new animal drug into interstate commerce (FDCA § 512(j); 21 USC § 360b(j)). To secure this exemption, the research sponsor must commit to meet the agency's investigational use testing requirements and file a "Notice of Claim Investigational Exemption for a New Animal Drug," commonly known as an INAD (21 CFR Part 511). The notice must identify the drug, the clinical investigator, and the sponsor, and describe in detail the nature of the investigation. The sponsor must assure the FDA that the investigator is qualified to conduct the study and evaluate the information obtained and that any unused supplies of the investigational drug will be appropriately disposed (CVM 1997a, 8). Under the INAD process, an "investigational animal" is any animal involved in the investigational phase of the development of a new animal drug, and can include animals that have been treated with the drug, those treated with placebos, and those otherwise used as comparators (CVM 1997a).[10]

Once an investigation or study begins, the sponsor must report to the FDA any evidence of a significant hazard related to the drug. Also, the sponsor may not commercially distribute or test market any new animal drug being studied under an INAD exemption. Failure to comply with these provisions can lead to the withdrawal by the FDA of the exemption and a decision not to rely on any of the information or data collected during the course of the study—a potentially costly and damaging consequence for the sponsor (21 CFR § 511.1(c)).

FDA investigators monitor the conduct of animal drug studies. The focus of this monitoring is threefold: the sponsor's compliance with its obligations under the agency's clinical investigation regulations; the investigator's compliance with those regulations; and the

10 For GE animals, then, "investigational animals" could include all animals involved in the study of the gene construct, such as those directly subjected to specific recombinant DNA (rDNA) techniques (whether or not the construct is incorporated), any offspring (regardless of their transgenic status), animals consuming milk from animals directly subjected to specific rDNA techniques or their offspring, and animals serving as experimental comparators.

investigator's compliance with regulations governing "good laboratory practices" (GLPs; 21 CFR Part 58).

NADA Submission, Review, and Approval

A new animal drug can be marketed only after the FDA approves a new animal drug application for the drug (21 CFR Part 514). The data resquirements to support the approval of an NADA are extensive. The FDCA expressly provides that an NADA must contain "full" reports of all clinical tests and investigations (FDCA § 512(b); 21 USC § 360b(b)). This includes protocols and all records of any tests performed on the new animal drug at the level of individual animal data, regardless of whether the data are favorable or unfavorable. The NADA submission must also contain a complete list of the components of the drug and a description of a validated analytical method capable of determining the quantity, if any, of the drug remaining in or on food (i.e., the residue) (21 CFR Part 514). The application must also contain any product labeling and an environmental safety assessment, per agency responsibilities under the National Environmental Policy Act (NEPA; 42 USC §§ 4321-4347).

Unless the existence of an NADA is publicly disclosed or acknowledged by the sponsor, the FDA must, as a matter of law, keep the existence of the application confidential until the drug is approved (FDCA § 301(j); 21 USC § 331(j)). Only upon approval of the NADA is its existence, unless otherwise divulged by the sponsor, made known to the public (21 CFR § 514.11(b)). However, if the existence of an application has been disclosed by the sponsor, the FDA may in its discretion divulge a summary of information appropriate for public evaluation. The FDA will not disclose the existence of a NADA before an approvable letter is sent to the applicant (21 CFR § 314.430). When an NADA is approved, a regulation to that effect is published in the *Federal Register,* and the FDA makes available on its web site a Freedom of Information Act summary of the data, the complete environmental assessment, and agency findings. Even upon approval, however, the contents of the NADA remain confidential—to reveal them at any time is unlawful.

Although the FDCA provides the FDA with a 180-day period to act upon an NADA, the agency rarely approves an application in that timeframe. The more usual situation is that the agency finds some portion of the application to be incomplete, and the applicant then goes about remedying the deficiency. Several of these review cycles may take place before an application is approved. The NADA for recombinant bovine somatotropin (rBST), for example, was under review for nearly six years prior to approval. The CVM has recently attempted to streamline its review of NADAs.[11] Also, the implementation of the recently approved Animal Drug User Fee Act (21 USC § 379(f) et seq.) may decrease the cycle time for reviews and possibly the number of cycles leading to an approval. The CVM's effectiveness and efficiency in regulating GE animals would likely be positively affected if increased resources were made available to the agency and as knowledge and experience are gained over time.

11 The CVM now encourages an "interactive" approach to the planning, research, and review of new animal drugs. The CVM seeks to interpose itself as early as possible in the process—often seeking to be involved even before product development is started so that a project undertaken has an increased probability of resulting in ultimate approval. (See, for example, CVM 2002.) Potential applicants are entitled under the FDCA to take part in pre-submission conferences, which the CVM encourages (FDCA § 512(b)(3); 21 USC § 360b(b)(3)).

Although the review of NADAs is the CVM's responsibility, the Center may also seek the advice of its expert advisory committee—the Veterinary Medicine Advisory Committee—or the Food Advisory Committee of the FDA's Center for Food Safety and Applied Nutrition.[12] Advisory committees respond to specific questions posed by the agency, and committee members provide their individual and collective opinions on those questions. The CVM is not required to follow their advice, although it usually does.

The FDCA does not provide any third-party right of review of NADA approvals. An approval may be contested in court only if the agency first denies a citizen petition contesting the approval (FDCA §§ 512(h) and 505(h); 21 USC §§ 360b(h) and 355(h); and 21 CFR § 10.30). Such contests are extremely rare and have never resulted in the reversal of an FDA decision to approve a new animal drug.

Post-Approval Controls

Extensive regulations govern sponsors' post-approval responsibilities for conventional new animal drugs. For example, the FDA requires that sponsors keep records and submit reports on information that may have a bearing on whether the approvals of their applications should be withdrawn or suspended (21 CFR §§ 510.300 and 514.80).[13]

On rare occasion in the human drug arena, the FDA has imposed post-approval monitoring programs as a condition of approval.[14] The authority to impose such controls also exists in the animal drug arena. However, the agency cannot require post-marketing monitoring unless it has reason to believe that safety cannot be ensured without such monitoring (21 USC § 360b). In several high-profile cases, including rBST, the agency has secured "voluntary" commitments from product sponsors to conduct post-approval monitoring or data collection and report the findings back to the FDA .

Pursuant to Section 704 of the FDCA, the FDA maintains broad inspectional authority over any facility where drugs are prepared, packed, held, or stored. The agency's ability to investigate extends to "all things" within the facility, such as records, files, complaints, and processing information (FDCA § 301(f); 21 USC § 331(f)).

Environmental Assessment

The submission of an INAD or an NADA requires a concomitant environmental assessment or a claim of categorical exclusion from such an assessment (21 CFR §§ 25.15, 511.1(b)(10),

12 For example, in December 2003 the FDA convened the Veterinary Medicine Advisory Committee to review a draft assessment of risks to animal and human health from animal cloning (CVM 2003a).

13 A sponsor must maintain all unpublished reports of clinical or other animal experience, studies, investigations, or tests of which it is aware concerning a new animal drug. The sponsor must also collect and maintain information concerning the quantity of the new animal drug produced and any changes from the conditions described in the original application. A change in the manufacturing or control procedures used in producing the drug, a change in the composition of the drug, or a change in intended use will likely require a new agency pre-approval. The sponsor is also required to maintain and report to the FDA about any mix-up of a new animal drug with another article, the failure of the drug to meet specifications, or any unexpected side effects, injury, toxicity, sensitivity reaction, or "any unexpected incidents or severity" with the use of the product (21 CFR § 514.80).

14 See, for example, the FDA's post-market restrictions on Accutane (http://www.fda.gov/cder/drug/infopage/accutane/smart.pdf).

and 514.1(b)(14)). This requirement is derived from NEPA (42 USC §§ 4321-4347). While NEPA lays out policies and standards for conducting environmental reviews, it does not require or authorize the FDA to make decisions that favor environmental protection over other relevant factors. Instead, NEPA merely requires agencies to consider environmental factors in their decision-making processes (*Environmental Defense Fund v. Mathews,* 410 F. Supp. 336 (D.C. 1976)).

The FDCA contains no reference to the environment and includes no environmental standard by which the FDA must make decisions. The law does define "safe" as having reference to "the health of man or animal," however (FDCA § 201(u); 21 USC § 321(u)), and the FDA has interpreted this authority to include environmental effects that directly or indirectly pose risks to the health of man or animals. Relying on this interpretation, the FDA has asserted that it has the power not only to impose conditions to ensure the mitigation of environmental impacts that may directly or indirectly harm humans or other animals, but also to refuse to approve a product if such environmental impacts prove to be unmitigatible (CEQ and OSTP 2001). The FDA has acknowledged that it does not have authority over environmental impacts that involve no health risk, however, such as impacts on scenic beauty (CEQ and OSTP 2001).

In approving NADAs for conventional animal drugs under Section 512 of the FDCA (21 USC 360b), the FDA has evaluated environmental safety and required data and information with regard to hazards to humans associated with manufacturing (e.g., hazards arising from occupational exposure to a new drug or its components or to emissions from a manufacturing facility that have the potential to harm people). The agency has also assessed hazards that may arise as a result of the administration of drugs to animals, such as disposal requirements for syringes used to administer rBST to cows. And, the agency has caused NADA sponsors to focus on potential harm to other animals arising from the use of a new drug.[15]

15 The recombinant animal drug rBST remains the best example of the agency's exercise of Section 360b's safety authority to assess environmental impacts and impose environmental mitigations. A review of the rBST precedent demonstrates the agency's view that its authority under Section 360b extends to environmental considerations. In April 1986, the Foundation on Economic Trends (FET) and others petitioned the FDA to prepare an "environmental impact statement" (EIS) concerning the commercial use of rBST. Under FDA regulations, an EIS would not normally be required until an environmental assessment was completed and demonstrated that significant potential environmental effects could not be ruled out. As a result, in September 1986, the FDA rejected the FET petition as untimely. In the process, the FDA noted that to the extent that the concerns raised by the FET were valid, they would be considered under the drug safety standards of 21 USC § 360b (FDA 1986). Years later, the agency did rely on the safety provisions of Section 360b to evaluate the environmental impacts of rBST on people and animals and to impose labeling restrictions and specific requirements with regard to syringe disposal.

Few other instances exist of the FDA's relying on Section 360b to address environmental issues. Perhaps the most notable involves the drug Warbex, a liquid form of the chemical famphur. Under the NADA process, the FDA approved Warbex for the topically applied systemic treatment of insect infestations of beef cattle, dry cows, and replacement heifers. After the drug was approved, numerous deaths of wild birds were observed as a result of the labeled use of the drug. Investigations also revealed instances of misuse of the product. As a result, the FDA, using Section 360b, imposed a warning label on the product to ensure proper usage and wild animal safety, specifically mentioning fish, birds, and other wildlife (CVM 1996). Also, in the case of the animal drug Ivermectin, the FDA relied on Section 360b to require that labeling provide aquatic toxicity warnings associated with the product.

The Labeling of Animal Drugs

The FDCA gives the FDA comprehensive authority over the labeling of new animal drugs and over human food derived from animals that are given such drugs. The fundamental thrust of the drug labeling provisions is to ensure that physicians and veterinarians correctly prescribe drugs and administer them safely (FDCA §§ 512(b)(1)(F), 512 (d)(1)(H), and 502; 21 USC §§ 360b(b)(1)(F), 360b(d)(1)(h), and 352). The agency has also employed its drug labeling authority to require warnings with regard to appropriate environmental use. The law's food misbranding provisions apply to the labeling of food products derived from animals treated with new animal drugs (FDCA §§ 403 and 201(n); 21 USC §§ 343 and 321(n)). The central purposes of these provisions are to prevent deception and to meaningfully inform, instruct, and warn consumers.

The FDA's Food Safety Authority

The general food safety authority of the FDCA was discussed at length in Chapter 3. It is reviewed briefly here, as the FDA could choose to rely on it for GE animals rather than on the new animal drug approval process. In short, the FDA does not review novel whole foods for safety before they go to market; instead, the agency relies upon its post-market enforcement authorities to take action against foods that are "adulterated" (FDCA § 402(a)(1); 21 USC § 342(a)(1)). It is the marketer's legal responsibility to ensure the safety of whole foods. The FDCA contains separate provisions for "food additives," substances that are deliberately added to foods. Food additives need to be approved by the FDA as safe before they can be marketed; a food that contains an unapproved food additive is considered to be adulterated and is illegal to market (FDCA §§ 402(a)(2)(c) and 409; 21 USC §§ 342(a)(2)(c) and 348). By definition, however, a substance added to a food is not a food additive if it is "generally recognized as safe" (GRAS; FDCA § 201(s); 21 USC § 321(s)). Foods containing GRAS substances are not subject to any mandatory pre-market safety review by the FDA. The agency is not required to determine whether an added substance is GRAS; a developer may self-affirm that a substance is GRAS (although such a determination could be challenged in an enforcement action by the FDA) (FDA 1997b). Thus, foods that contain substances believed by the marketer to be GRAS may go to market without prior FDA review or approval.

THE POTENTIAL APPLICATION OF THE FDCA TO GE ANIMALS

This section discusses how the FDA could use its new animal drug authority to regulate GE animals. The possibility of the agency employing only the FDCA's food safety authorities is also discussed.

New Animal Drug Authority

According to the CEQ-OSTP case studies, GE animals can be viewed as containing new animal drugs because the bioengineering process is intended to alter the "structure or function" of the animals. The inserted genetic constructs and their expression products can be considered drugs, and the animals themselves can be regulated because they have the potential to enter the food chain (CEQ and OSTP 2001, 13-14).[16]

16 Although gene-deletion techniques that affect a change in an animal may not fit the "drug" definition as clearly as the insertion of novel genes, the intent of a gene deletion to affect the structure or function of the animal could arguably provide a sufficient hook for regulation.

The FDA has informally indicated that it will regulate the genetic engineering of animals using the FDCA's new animal drug approval provisions. The CVM in 2003 sent a letter to Land Grant Universities conducting research on GE animals informing them about the applicability of the FDCA (in particular the INAD provisions) to these animals (CVM 2003b).[17] To date, however, no GE animals have been approved by the FDA, and the agency has not developed any regulations or public guidance that provide a clear illumination of how (or even if) the NADA process will apply to GE animals.[18] Aqua Bounty Technologies, a Massachusetts-based biotechnology company, has announced that it has a fast-growing GE salmon currently under review at the CVM (Martin 2003). Also, the agency reportedly has several INADs open on investigational GE animals. However, how the FDA will apply its regulations and standards for conventional new animal drugs to GE animals remains unclear.

Under the new animal drug rubric, it presumably would be unlawful to market a GE animal without first submitting an NADA to the FDA and securing the agency's approval of the application (21 USC § 360b(a)(1)). The safety standard traditionally employed by the FDA would ensure that the genetic modification process is safe for the animal and that products from the animal are safe for human consumption, if that is their intended use. Scientific information demonstrating effectiveness would have to show that the genetic modification process has the desired effect on the animal—for example, that the process results in an animal that does in fact grow faster or is more disease-resistant than its conventional counterpart.

The existence and contents of NADAs for GE animals would, by law, be treated with the same confidentiality as those for conventional new animal drugs, with no opportunity for prior public review or comment. Scientific advisory committees may be used for new GE animals undergoing the review process, as the FDA is especially likely to use such committees if a new animal drug raises complex or sensitive scientific issues. The extensive post-approval responsibilities of the sponsors of conventional new animal drugs would presumably also apply to the sponsors of GE animals.

Precisely how other procedures and requirements for new animal drug approval would be applied to GE animals remains unclear in the absence of FDA guidance.

Food Safety Authority

Instead of using its new animal drug approval authorities, the FDA could potentially consider only the food safety aspects of GE animals entering the food supply, under its general food safety authority (FDCA §§ 402 and 409; 21 USC §§ 342 and 348). By treating GE animals solely as food, the FDA could adopt an approach similar to the one it uses with respect to foods derived from GE plants. Genetic constructs and their expression products could be considered potential food additives, unless they were substances that were sub-

17 The letter reminded investigators and sponsors that investigational animals should not enter the human food or animal feed supplies unless CVM approval is granted (CVM 2003b).

18 In December 2003, the FDA declined to regulate the Glofish—an ornamental zebra fish modified through genetic engineering to glow—because it was not intended for food use and would not pose any greater environmental risk than its unmodified counterparts. The FDA found "no reason" to regulate the Glofish "in the absence of a clear risk to the public health" (FDA 2003a).

stantially similar to substances already consumed in food, in which case the FDA might presumptively categorize them as GRAS. For whole foods, the composition of the food would need to be "as safe as" comparable food. If the FDA were to take such an approach, it would likely institute a voluntary pre-market consultation program like the one it has in place for foods derived from GE plants (FDA 1992 and 1997a).[19] While this approach would be more consistent with the FDA's 1992 policy guidance for crops derived from GE plants, it would clearly not address questions about animal safety or environmental risks. In addition, this approach would appear to depend upon an FDA determination that genetic modifications of animals do not constitute altering the "structure or function" of those animals, a finding that could be difficult to sustain.

THE USDA

This section describes the animal quarantine (AQ) laws that were consolidated in the new Animal Health Protection Act, as well as the meat inspection laws, the Plant Protection Act, the Animal Welfare Act (AWA), and the Animal Damage Control Act. The next section will discuss how these laws might theoretically apply to GE animals, with particular emphasis on authorities that could be used to address some of the food safety, animal health and welfare, and environmental issues associated with the genetic engineering of animals.

The Animal Quarantine Authorities and the AHPA

Since 1884, several animal quarantine laws have been used to control and eradicate contagious, communicable diseases and pests of livestock and poultry. In 2002, Congress consolidated the AQ laws into the Animal Health Protection Act (7 USC § 8301 et seq.). The AHPA was enacted, in part, to address gaps that had previously been identified in the AQ laws.[20]

Under the AQ laws, APHIS has broad power and authority to regulate animals, articles, and means of conveyance moving into the United States and interstate in order to prevent the introduction and dissemination of livestock diseases and pests (e.g., 7 USC §§ 8303, 8305, and 8306).[21] These quarantine laws and their regulations were established to protect the economic interests of U.S. agriculture; they have not historically been used to address human food safety concerns or broad environmental issues.[22] APHIS has three basic types

19 For meat and poultry products, the FSIS would be required to enforce its meat and poultry inspection authorities in manner that is consistent with FDA reviews, whether those reviews are completed via a mandatory approval process or a voluntary pre-market notification process (21 USC § 601(m)).

20 For example, before the AHPA, in order to take action under its general authority, APHIS had to find that animals were diseased or had been exposed to disease (21 USC §§ 104, 105, and 134a). Under the AHPA, APHIS only has to find that the animals may have been so exposed or may be carrying the disease or pest (7 USC § 8306(a)(1)(B)). Even under the AHPA, however, APHIS cannot take action under its general authority with regard to *other* animals that may have been associated with the animal, article, or means of conveyance of concern (§ 8306(a)).

21 Technically, the laws give the Secretary of the USDA authority to act. The Secretary in turn delegates that authority to APHIS (7 CFR §§ 2.22 and 2.80).

22 APHIS has used the AQ laws to address human food safety concerns only where there was also a livestock disease concern. For example, asserting its authority under the AQ laws, APHIS published *Salmonella enteritidis* regulations concerning table eggs (17 CFR § 82.30) in order to prevent human food poisoning. The regulations were upheld as being within APHIS's authority (*Rose Acre Farms, Inc. v. Madigan,* 956 F2d. 670 (7th Cir. 1992) cert. denied 506 US 820).

Figure 4.2 The USDA's Three Types of Authority to Regulate Livestock Diseases and Pests

APHIS's **general authority** allows it to regulate the importation and interstate movement of animals, articles, and means of conveyance that may be diseased with, exposed to, or carrying a livestock disease. The agency is authorized to hold, seize, quarantine, treat, destroy, dispose of, or take other remedial action with regard to animals, articles, or means of conveyance that are in or have moved into the United States or interstate which it believes may have been diseased with, exposed to, or carrying a livestock disease at the time of their movement into the United States or interstate, or were moved in violation of regulations under the AHPA. APHIS is also authorized to take action with respect to animals and their progeny that are imported or moved interstate in violation of the AHPA, any regulation, or any order issued by the Secretary.

If APHIS needs additional funds to carry out activities to control or eradicate a livestock disease, it can declare an **emergency** that allows it to transfer funds from any agency or corporation of the USDA for the purpose of controlling or eradicating the livestock disease or pest.

The states are responsible for taking measures to prevent the *intra*state spread of livestock diseases. If APHIS finds that a state is not taking adequate measures to prevent the spread of a livestock disease, it may declare an **extraordinary emergency** and take action on intrastate matters (7 USC §§ 8303, 8305, 8306, and 8316).

of authority it can use to regulate livestock diseases and pests: general authority, emergency authority, and extraordinary emergency authority (§§ 8303, 8305, 8306, and 8316). (See Figure 4.2.)

To control animal diseases, particularly from importation into the United States, the AQ regulations prohibit or restrict the importation of animals, articles, and means of conveyance that are from (or have had any association with animals, articles, or means of conveyance from) countries infected with diseases or pests exotic to the United States (9 CFR Part 93). The regulations are most stringent concerning those diseases or pests that experts do not understand well or do not know how to prevent from spreading. Strict procedures must be followed before importing, at the border, and after entry.[23] If the procedures are not followed, or if any of the conditions are not met, then the animal is typically denied entry into the United States (§ 93.103 and Parts 204, 304, 404, 504, 704, and 802).

In order to prevent the spread of diseases to other livestock, APHIS may cooperate with states to use the states' authority to contain or eradicate an animal disease or pest, or it

23 Procedures are frequently required to be carried out in foreign countries by appropriate government authorities in order for animals to be eligible for importation into the United States (e.g., 9 CFR § 93.101 and Parts 104 and 301). In addition, APHIS often requires that import permits, which must accompany imported animals, include such procedures (§ 93.103 and Parts 204, 304, 404, 504, 704, and 802). These procedures have included inspections, tests, quarantines, treatments, and other procedures to eliminate diseases and pests and to ensure that they are not present when the animals are imported into the United States. The same procedures can be, and often are, repeated at the border or while animals are en route to or in quarantine in the United States and before they are allowed to enter commerce in the United States. There is also authority to require that imported animals be kept under quarantine after entering the United States, including permanent post-entry quarantine.

may quarantine a state or portion of a state to prevent the dissemination of a disease or pest (7 USC §§ 8305, 8306, and 8310; 21 USC § 123). However, such a quarantine only prevents the *inter*state movement of regulated animals and products; it does not stop *intra*state movement. Usually, a state is willing to cooperate with APHIS to prevent intrastate movement in order to encourage APHIS not to quarantine the entire state.

APHIS also uses its quarantine authority to prevent the interstate movement of animals that have not been identified, tested, inspected, or treated in a specified manner. Accredited veterinarians perform many of these functions before issuing health certificates allowing for the interstate or international movement of such animals (9 CFR Parts 71-85).[24]

APHIS must declare an extraordinary emergency in order to enforce a quarantine of less than an entire state. To do this, APHIS has to determine that a disease or pest of livestock exists in the United States that threatens the livestock of the United States. The agency is not allowed to hypothesize that such a disease or pest may be present. The agency also has to find that adequate measures are not being taken by the state, or other political subdivision, to control the animal disease or pest. APHIS has to publish the finding and its basis in the *Federal Register*. After APHIS declares an extraordinary emergency, it may hold, seize, treat, destroy (including preventative slaughter), or apply other remedial measures as it determines necessary to prevent the dissemination of the pest or disease (21 USC § 8306(b)).

The agency is authorized to order the owner of any animal that has moved interstate (or that is subject to a declaration of extraordinary emergency) to maintain the animal in quarantine, dispose of it, or take other remedial action to prevent the dissemination of the disease or pest. If the owner fails to take the prescribed action, APHIS may take the action and recover from the owner the cost of the action and the cost of any associated care, handling, or disposal (§ 8306(c)).

APHIS is required to pay the fair market value, as determined by the agency, for any animal, product, or article that it destroys or requires to be destroyed under the AHPA, minus any compensation received from any other source. However, APHIS is not required to pay compensation for animals or their progeny moved in violation of the AHPA or its regulations (§ 8306(d)). While it can be argued that the true value of a diseased or exposed animal is nil, or even negative, APHIS has historically paid the fair market value of a healthy animal in order to obtain the cooperation of affected owners and the industry in its eradication efforts (APHIS 2001). When APHIS declares an emergency because of an animal disease, it can transfer money from one agency or account within the USDA to another for the purpose of monitoring, controlling, and/or eradicating the disease (21 USC § 8316(b)).[25]

24 Intrastate health certificates are often required by states, and can also be required by APHIS for intrastate movements pursuant to an extraordinary emergency (21 USC § 8306(b)).

25 Generally, this involves a transfer from the Commodity Credit Corporation (CCC) to APHIS for the control and eradication of an animal disease emergency. However, the money is not required to be from the CCC and is not required to be transferred to APHIS. It could be transferred from any account or corporation to any other agency within the USDA, as long as it is for the control or eradication of a disease or pest of livestock.

Under the AHPA, APHIS also has broad authority to conduct inspections without warrants.[26] Violations of the AHPA or its regulations are punishable with civil penalties of up to $50,000 for an individual or up to $250,000 in the case of any other person (7 USC § 8313(b)). APHIS can also refer cases to the Department of Justice for criminal prosecution if a person knowingly violates the law or its regulations (§ 8313(a)). In most situations, the agency chooses to pursue civil rather than criminal penalties.

The Meat Safety Laws

The USDA's Food Safety and Inspection Service administers the Federal Meat Inspection Act (FMIA; 21 USC § 601 et seq.) and the Poultry Products Inspection Act (PPIA; 21 USC § 451 et seq.). As their names imply, these are primarily inspection laws. They make it unlawful to sell any meat or poultry product unless it has been inspected and passed by the FSIS. The FSIS is required by these laws to conduct both ante-mortem and post-mortem inspections of most types of animals offered for slaughter[27] and daily inspections in all plants that process meat and poultry products. Meat and poultry slaughter and processing plants are not allowed to operate unless they meet basic requirements relating primarily to their ability to operate under good sanitary conditions. The meat inspection laws could theoretically be used to help enforce an identification and tracking system for GE animals.

The inspection laws make the FSIS the final gatekeeper to the marketplace for meat and poultry products. The standards that the FSIS applies in playing this gatekeeper role are grounded in the statutory definitions of "adulteration" and "misbranding" (21 USC § 601(m) and (n)). In order to "pass" a product and thus allow its sale, the FSIS must find that the product is neither adulterated nor misbranded. Adulteration includes, for example, the presence of visible contamination on carcasses that might make the resulting food unsafe or unwholesome. The FSIS has established criteria that it applies to determine whether a product will be deemed adulterated, and FSIS inspectors reject carcasses that violate these criteria. Carcasses that bear fecal contamination or visible signs of disease are commonly rejected on this basis (§ 601(m) and (n)).

The FSIS's inspection program also enforces some of the food safety standards and decisions made by the FDA and the Environmental Protection Agency (EPA). For example, both the FMIA and the FDCA deem food adulterated if it contains levels of environmental contaminants—such as lead, mercury, and dioxins—that are potentially harmful to health (§§ 601(m)(1) and 342(a)(1)). The FDA customarily sets limits on the permissible presence of such chemicals, and the FSIS enforces the these limits by periodically sampling and

26 APHIS has authority to stop and inspect, without a warrant, any person or means of conveyance moving into the United States to see if they are carrying any animal or article regulated under the law. The agency is also authorized to stop and inspect without a warrant any person or means of conveyance moving interstate, or intrastate under an extraordinary emergency, upon probable cause to believe that the person or means of conveyance is carrying any animal or article regulated under the law. There is also authority for APHIS to enter with a warrant any premises in the United States for the purpose of making inspections and seizures (7 USC § 8307).

27 The FMIA and PPIA only apply to certain enumerated animals and not to all animals offered for slaughter. For example, bison and certain bison-cattle cross-bred animals are inspected by the FSIS on a voluntary, fee-for-service basis and not under the mandatory inspection program enforced by the FSIS (21 USC § 601(j)).

testing carcasses as part of its inspection program (§ 601 et. seq.; FSIS 2001). Similarly, the FDA is responsible for approving food and color additives for use in meat and poultry products (21 CFR § 71.20), and the EPA establishes permissible limits for the presence of pesticide residues in food (21 USC §§ 301-392). The meat and poultry inspection laws deem food adulterated if it contains levels of food or color additives or pesticide residues that exceed the levels approved by the FDA or EPA (21 USC § 601). The FSIS is responsible for enforcing the FDA's and EPA's standards in these areas with respect to the meat and poultry products leaving FSIS-inspected facilities (§ 601(m)).

While the FDCA deems food adulterated if it contains an unapproved animal drug or conversion product thereof (§ 342), there is no adulteration provision in the FMIA or PPIA that makes it illegal per se for the residue of an animal drug to be present in meat or a meat product. Thus, while the FDA has authority to enforce a per se prohibition on the presence of an unapproved animal drug in meat or other food under the FDCA, the FSIS has no such authority under the FMIA or PPIA.

The Animal Welfare Act

The Animal Welfare Act, administered by APHIS, is intended to ensure (among other things) the humane care, treatment, and handling of certain animals intended for use in research (7 USC §§ 2131 and 2135). Theoretically, people, facilities, and institutions that do research on GE animals could be subject to the requirements of the AWA under certain conditions.

Under the AWA, dealers, exhibitors, and research facilities must be licensed or registered with the USDA (9 CFR Part 2). A "research facility" is defined to include any institution, organization, or person that uses or intends to use live animals in research, tests, or experiments, and that purchases or transports live animals in commerce, or receives a grant, award, loan, or contract from a department, agency, or instrumentality of the United States. APHIS may exempt, by regulation, biomedical research facilities that do not use live dogs or cats, or that do not use substantial numbers of other animals (9 CFR § 1.1).

The regulations define an "animal" as any warm-blooded animal, but they specifically exclude birds, rats and mice bred for research, horses not used for research purposes, and other farm animals, such as livestock and poultry, used or intended for use for improving animal nutrition, breeding, management, or production efficiency, or for improving the quality of food or fiber (§ 1.1).

The Plant Protection Act

APHIS's authority to regulate plant pests under the Plant Protection Act (7 USC § 7701 et seq.) was discussed at length in Chapter 2. Prior to the 2000 enactment of the PPA, the scope of the agency's plant pest authority was limited to microorganisms, insects, other invertebrate animals, and parasitic plants (7 USC § 150aa(c)(1994)(repealed)). The PPA added "nonhuman animals" (7 USC § 7702(14)(B)) to the list of organisms that qualify as plant pests. Since many animals have impacts on plants—including cattle via grazing, for example—the scope of this change will remain unclear until APHIS defines through regulations how it intends to apply the law. To the extent that animals (including GE animals) are defined by APHIS as plant pests, the agency would have the same broad authority to regulate the interstate movement and "release into the environment" of animal plant pests that it has with insects and plants that harm crops and plants.

The Animal Damage Control Act

The Animal Damage Control Act (7 USC § 426) has historically provided APHIS with authority to assist in the control of wild animals that carry diseases like rabies, and wild animals that otherwise prey on or injure livestock and crops, such as coyotes and blackbirds. In 2000, Congress replaced the previous language of the law with a short section that enables APHIS to "conduct a program of wildlife services with respect to injurious animal species and take any action the Secretary considers necessary in conducting the program." The amendment also directed APHIS to "administer the program in a manner consistent with all of the wildlife services authorities in effect on the day before October 28, 2000." It is conceivable that this authority might be used to control or eradicate GE animals that have escaped and pose a risk to agriculture, though the limitations of this interpretation are noted below.

APHIS'S POLICIES REGARDING GE ANIMALS

At present, APHIS has few policies or regulations specific to GE animals.[28] Given the absence of established APHIS policy, the question of how or whether any of the agency's authorities noted above could be used to regulate GE animal issues related to food safety, animal health and welfare, and environmental impacts is discussed in the following section.

Issues and Concerns regarding the Existing System

This section describes issues and concerns regarding the existing, proposed, and possible regulatory systems governing GE animals. The section is split into two main parts: the first covers issues relating to the FDA's authorities, the second concerns the USDA's authorities. In each part, the issues are organized into five categories: overall responsibility and legal authority; pre-market authority; post-market authority; clarity, transparency, and public participation; and coordination. In the FDA section, most of the discussion considers the new animal drug approval process, as the agency's food safety authorities were addressed at length in Chapter 3.

THE FDA

Overall Responsibility and Legal Authority

This section explores two issues relating to the FDA's responsibility and legal authority under the FDCA: (1) issues that arise from regulating GE animals under the new animal drug rubric, including the agency's authority to address potential environmental concerns relating to GE animals; and (2) issues relating to an alternative regulatory approach in which the FDA would regulate only food safety aspects under its general food safety authority.

Regulating GE Animals under the New Animal Drug Rubric

The interpretation that genetic constructs inserted into animals, and their expression products, constitute new animal drugs under the FDCA expands the traditional definition of drug.

28 As noted previously, APHIS has addressed insects that are plant pests under the PPA (1995). Under that authority, APHIS sought comment on a proposed environmental impact statement for a GE pink bollworm (2002b). The FSIS has also provided guidance on GE animals (1997a and 1997b).

Certainly conventional animal drugs do not cause animals to have permanent, inheritable genetic alterations. There is no evidence that Congress intended to provide the FDA with authority to regulate GE animals under the new animal drug approval provisions of the FDCA.

Such an interpretation, however, is not inconsistent with agency precedent and practice. The FDA has often sought to accommodate new scientific insights and understanding and to incorporate innovation and advancements in technology. To determine whether or not a product is subject to FDA jurisdiction, the agency must judge the "intended" use of the product. In the context of GE animals, the requisite level of "intent"—the intent to affect the bodily function of an animal—could be interpreted as clearly established. Moreover, courts have upheld expansive definitions of the term "drug."[29] The agency's creative interpretation of its statutory authority to adjust to scientific progress has also been consistently upheld by the courts. Deference to agency decision making is particularly strong in areas such as biotechnology that involve technological advances falling within the agency's expertise (*Alliance for Biointegrity v. Shalala,* 116 F. Supp.2d 166 (D.C.C. 2000)). The courts could well defer to the agency's decision making regarding the drug status of a genetic construct used to genetically engineer animals.

Questions exist, however, about how well the new animal drug rubric fits with genetic engineering. A number of the regulations, such as those governing drug labeling, good laboratory practices, and good manufacturing practices (GMPs) make little sense in the context of GE animals. For example, the labeling of GE animals and their progeny raises different issues than the labeling of conventional animal drugs, which are intended for use by veterinarians. For example, what would technically be labeled—the inserted gene construct, the expression product of the gene construct, or the GE animal itself? Would only the initial transformed animal be covered, or would subsequent generations also be covered? And whatever the labeled item may be, how can it practically be labeled? The adulteration and misbranding provisions specify quality, cleanliness, packaging, label placement, and even typeset criteria that do not readily translate to the realities of a living animal (FDCA § 502(e); 21 USC § 352(e)). For instance, can a GE animal be prepared, packed, or held in conditions free of contamination? Or, if a label is required, what constitutes conspicuous placement so it is likely to be read by the ordinary individual under customary conditions of purchase and use (FDCA § 502(c); 21 USC § 352(c))?

Legal and practical issues also exist about whether and how the FDA can oversee the safe and effective use of GE animal progeny. The law applies to the intended use of a substance as a drug. Are subsequent generations of GE animals the "intended use" of the substance?

29 Since the first definition of "drug" appeared in the Pure Food and Drugs Act of 1906, the definition has regularly been expanded to include substances not familiarly categorized as drugs. The Supreme Court endorsed this trend in 1969 in *United States v. Article of Drug...Bacto-Unidisk* (394 U.S. 784), when it found that a cardboard disk impregnated with reagents and marketed as a mechanism for diagnosing sensitivity to antibiotics constituted a "drug." The court concluded that the literal language of the law could be interpreted in a manner "broader than any strict medical definition might otherwise allow." The court's rationale was that the FDCA should be given a liberal construction in order to best protect public health. In addition to *Bacto-Unidisk*, a key precedent in this regard is *United States v. Dotterweich* (320 U.S. 277 (1943)). In that case, Justice Felix Frankfurter noted that the purposes of the FDCA touch all phases of the lives and health of people—people who under modern industrialism are largely beyond self-protection. Frankfurter urged that the purposes of the legislation should "infuse" its construction and that the law should be treated as a "working instrument of government" and "not merely as a collection of English words" (320 U.S 280 (1943)).

The FDA could argue that persons can be held to "intend" the reasonably foreseeable consequences of their actions (21 CFR § 201.128), but whether a court would sustain such an argument would likely depend on the facts of the specific case.[30]

An additional issue is that some GE animals may be exempt from the FDA's pre-market approval process on the grounds that the genetic constructs and the expressed products in the animals are substances generally recognized as safe and effective.[31] Nucleic acids are ubiquitous, and expression products like growth regulators and hormones have been, in some instances, well characterized and used as conventional drugs, which may provide some sponsors with an opportunity to pursue GRASE status for some GE animals or products derived from them. Given the relative novelty of genetic constructs, however, and the potential of such constructs to have unintended effects that could affect animal health, the argument that any such application would meet all of the requirements of the GRASE standard could be difficult to prove.

Even if the FDA is able and willing to apply the FDCA's new animal drug provisions to GE animals, the agency may not have the authority to consider the full range of environmental risks posed by such animals. As noted previously, the FDA has interpreted its authority to ensure that new animal drugs are "safe" as encompassing the power to consider and evaluate environmental effects that could directly or indirectly affect the health of people and other animals (CEQ and OSTP 2001).[32] However, the agency has acknowledged that it does not have authority over environmental impacts that do not raise animal or human health issues (CEQ and OSTP 2001). As a result, it may not be able to consider ecosystem effects, such as effects on non-animals (e.g., plants and microorganisms) and natural resources (e.g., water and soil). A recent NRC report argued that this weakness in the new animal drug provisions (as well as similar weaknesses in other agencies' authorities) must be remedied for the regulatory system to cover the range of environmental risks that might be posed by GE animals (2002a, 114-115).

The FDCA also lacks a statutory standard for making regulatory decisions about environmental risks. While the FDA must consider environmental issues under its NEPA obligations, NEPA does not direct the FDA as to how to take environmental considerations into account in making regulatory decisions. For example, if the FDA were to determine that a given GE animal posed a significant, non-health-related environmental risk, NEPA would not preclude the agency from granting a permit or a license.

The agency's relative lack of experience in environmental decision making also raises the question of whether the FDA is the appropriate agency to consider environmental risks from GE animals (NRC 2002a).

30 "[T]he law presumes that every man intends the legitimate consequences of his own acts" (*Agnew v. United States*, 165 U.S. 36, 53 (1897)).

31 To establish that a product is GRASE, the product must have a general reputation within the scientific community for safety and effectiveness that is clearly documented by at least the same amount of evidence necessary to obtain approval of the product in the first instance. Moreover, that evidence must be public and generally available to the scientific community (CVM 1997b).

32 In the rBST case, the FDA considered, among other things, the impact of drug approval on land use patterns, water quality, carbon dioxide emissions, and used syringe disposal. The FDA approved rBST as a new animal drug in 1993, and the agency's assertion of its environmental authority in the case has not been challenged.

Finally, an issue exists about whether the new animal drug approval procedures provide the FDA with sufficient authority to regulate the environmental releases of GE animals in preliminary research—before an INAD process is initiated. Even small-scale releases of GE animals have the potential to spread unwanted genes into related wild populations, particularly with birds, insects, fish, and other animals that are mobile and easily become feral (NRC 2002a). The FDA maintains some control of experimental animal drugs though the INAD process, but it is unclear precisely at what stage in the development of a transgenic animal the submission of an INAD is required. The FDA has recognized that some preliminary laboratory testing of GE animals—the testing that precedes a manufacturer's decision as to whether it has a commercially viable product—may be conducted prior to the submission of an INAD notice (21 CFR § 511.1(a)). Clearer agency guidance and instruction may be needed for determining when in the development of a transgenic animal an INAD must be opened. Once an INAD is initiated, the FDA has in place fairly well-established procedures (for conventional animals drugs) for overseeing the investigation.[33]

Regulating GE Animals under the FDA's General Food Safety Authority

As an alternative to regulating GE animals under the new animal drug approval provisions, the FDA could decide as a policy matter to regulate only the food safety aspects of food derived from GE animals, under its general food safety authority (21 USC §§ 342 and 348). If the agency took this route, it could adopt a GRAS/food additive approach to food derived from GE animals similar to the one it has adopted for food derived from GE plants (FDA 1992 and 1997a).

Under this approach, developers of GE animals would benefit by forgoing the presumably more time-consuming, mandatory pre-market approval process under the new animal drug rubric. Also, the FDA would need to divert fewer resources toward overseeing the development and commercialization of GE animals, as those animals developed for nonfood uses—e.g., pets, ornamental animals, and animals modified to produce drugs and industrial chemicals—would fall outside the regulatory influence of the FDA and the NADA process. This approach could significantly expedite the commercialization of GE animals intended for food use and may be considered scientifically defensible on a case-by-case basis.

Assuming that most food derived from food-use GE animals would be GRAS, however, taking a food-safety-only approach would raise many of the same public policy issues discussed in Chapter 3. For example, concerns about the lack of a pre-market approval requirement for foods from GE plants would apply equally to foods from GE animals. As a result, this approach would likely meet resistance from those who have raised concerns about the voluntary pre-market notification approach for GE plant products.

In addition, this approach would not address environmental or animal safety issues at all. If the FDA does not address these issues through the new animal drug process, it is unclear whether they can be addressed and regulated through other agencies, such as APHIS. As noted

33 Once an INAD has been opened on a GE animal, the FDA attempts to work closely with investigators to ensure the appropriate disposition of the animals. Among the key issues that are monitored are the maintenance of adequate records and the review of any environmental assessment conducted (or any request for a categorical exemption). Monitoring may also include unannounced inspections of the facility or facilities at which INAD-related investigational research is conducted (21 CFR § 511.1).

in more detail below, none of APHIS's laws provide clear authority for that agency to consider environmental issues associated with GE animals. Also, the ability of APHIS to address larger public health concerns under the AHPA (e.g. the containment of animals for the purpose of ensuring the safety of the food supply) is even less clear than under the PPA's noxious weed provisions, as the AHPA does not give APHIS broad public health authorities.

A food-safety-only approach also would not provide the FDA with authority to track what is entering the food supply, nor would it give the agency notice about whether substances being produced by nonfood-use GE animals—including pharmaceuticals and industrial chemicals—are entering the food supply.

Pre-Market Authority under the New Animal Drug Rubric

The FDCA's new animal drug provisions constitute a mandatory pre-market approval process that considers food safety, animal health, human health, and potentially some environmental issues. This assumes that the FDA's position that the genetic engineering of an animal constitutes a new animal drug would hold up in court if challenged. And, as noted above, the extent of the agency's authority to make regulatory decisions based on environmental considerations (beyond human and animal health effects) is unclear.

Post-Market Authority under the New Animal Drug Rubric

It is relatively clear that, for food safety and animal safety issues under the new animal drug approach, the FDA can require and enforce post-market controls should a problem arise with a new animal drug. To the extent that the FDA can legally exercise control of environmental assessments, requirements, and restrictions, the agency should be able to implement similar post-market controls for these issues.

Should the agency proceed with implementing the new animal drug approach, it will need to issue guidance on a number of post-market regulatory issues related to GE animals. Presumably, the producer of a GE animal (like the producer of a conventional animal drug) would be subject to post-marketing inspection controls and requirements. According to the CEQ-OSTP cases studies, the FDA will routinely (i.e., every two years or more frequently "for cause") inspect GE animal production facilities to ensure that all requirements are being followed, including requirements regarding recordkeeping and animal identification and tracking (CEQ and OSTP 2001). However, specific agency guidance is lacking on just how these authorities can be tailored to the regulation and monitoring of GE animals and products derived from them. Can only a facility itself, and its control mechanisms for GE animals, be monitored, or can the FDA's authorities also apply to individual GE animals? Can individual animals be identified, tracked, and monitored, and, if so, how can this feasibly and effectively be done? Can and should the FDA exercise control over subsequent generations of offspring developed from a previously approved GE animal, and, if so, how are these animals to be feasibly regulated?

Systems for ensuring that unexpected or adverse events become known to product sponsors and thus reported, as required, to the FDA have evolved over time to become reliable indicators of problems in the new drug and new animal drug arenas (FDA 2003b). Although reportable events in the context of GE animals will likely involve many of the same types of observations that currently take place for conventional animal drugs, the

agency may need to tailor the system for GE animals to account for the potential impact of these animals on the environment, to ensure that any problems are identified and reported.

It is unclear whether the FDA could impose post-marketing monitoring on GE animals for food safety or environmental impacts. The agency does not routinely apply such post-market requirements, except for a few cases in which novel or specific risks were present or anticipated. For example, for rBST and the fat substitute olestra, the FDA secured commitments from the product sponsors to conduct thorough post-market research and monitoring and to collect data and information on the possible impacts to people and/or animals presented by the extended use of and exposure to the product.[34] In light of these precedents, the agency could opt for comparable voluntary commitments regarding post-market surveillance and data collection upon approval of an NADA involving GE animals. It is unlikely that a sponsor would object to such surveillance provisions, if these steps were deemed important by the FDA for granting market approval.

Another key unanswered question is whether and how the FDCA's labeling authority could be used to develop, mandate, and enforce animal identification and tracking systems (if such measures are deemed warranted), particularly for research animals, GE animals not intended for the food supply, and the progeny of GE animals. Presumably, GE animals approved for food use would not require any special handling requirements for safe use as food, and, therefore, would not require labels to describe safe use practices. In the event that a GE animal approved for food use posed an *environmental* risk that required a label to instruct safe use, however, a number of questions arise. The matter is further compounded in instances in which GE animals not intended or not approved for the food supply (and their progeny) would need instructions for safe use or special handling requirements. In these cases, the FDA would need to coordinate its authorities with other agencies, such as those in the USDA.[35] If it is deemed either necessary or desirable to institute an identification and tracking mechanism for some or all GE animals, both regulations and a relevant monitoring and enforcement infrastructure would need to be developed.

Clarity, Transparency, and Public Participation Under the New Animal Drug Rubric

Given the absence of guidance from the FDA as to whether and how GE animals will be regulated under the new animal drug approval provisions of the FDCA, there is an obvious lack of clarity. Key questions, some of which have been identified previously, need to be answered. For example: What products and techniques will be covered? What standards and criteria will be used to determine a product's safety? What defines a "GE animal," a "no-take animal,"[36] and an "escape?" When in the course of research on GE animals will

34 In 2001, the FDA signaled a similar expectation in the context of two animo acids in infant formula that the agency acknowledged to be generally recognized as safe (AAP 2002).

35 The recent announcement that the USDA will consider a tracking and identification system for cattle in response to concerns about bovine spongiform encephalopathy ("mad cow disease") would clearly be relevant (USDA 2003).

36 In general, a "no-take animal" is an animal produced as a result of an attempt to produce a transgenic animal but in which the genetic alteration was not successful or not inherited, and the animal has no detectable genetic code alteration.

an INAD be required and when will an NADA be required? How will existing GLP and GMP requirements be adapted to cover GE animals and their byproducts? How and when will animal identification and tracking occur?

The relative lack of transparency and opportunity for public comment in the new animal drug approval process is another issue. As mentioned previously, the FDCA's new animal drug provisions were not designed for either transparency or public participation. Instead, confidentiality was intended to protect innovation and provide research and development incentives to drug manufacturers and, ultimately, beneficial products to the public. Complete confidentiality thus was accorded a company's decision to seek new animal drug approval and every following step. As a result, it is in most cases a violation of federal law to divulge even the existence of the submission of an INAD or an NADA. Even upon approval, the data supporting authorization remain confidential unless made publicly available by the manufacturer. The statute also does not provide any meaningful opportunity for the public to contest an agency's approval. While the confidential nature of the NADA process may provide innovators of conventional animal drugs with an opportunity to protect intellectual property in a highly competitive marketplace, in the context of GE animals it may also work against fostering public acceptance, and therefore market acceptance.

Interestingly, the confidentiality restrictions of the NADA are in conflict with the public notice and comment requirements for and EIS under NEPA, which poses a difficult conundrum for the FDA, not only in the case of GE animals, but technically also for conventional animal pharmaceuticals approved under the NADA process (40 CFR Parts 1500-1508).

Coordination

The FDA faces challenges on many fronts with regard to coordination with other agencies that may have concerns about GE animals. Since the FDA's mandate is not steeped in the larger ecological concerns that will be posed by some GE animals, the agency may need to work closely with state and federal agencies—such as the U.S. Fish and Wildlife Service (FWS), the National Marine Fisheries Service (NMFS), and state wildlife agencies—to enhance and ensure the adequacy of its assessments and decisions. Also, the FDA may need to augment its own resources and staff in this regard. Similarly, in order to ensure that unapproved GE animals or those not intended for the food supply (and their respective progeny) are appropriately handled, the FDA will need to work closely with state and federal meat inspectors (including the FSIS) to protect the safety of the food supply. Also, APHIS, and the USDA in general, may have livestock safety and marketing concerns that fall outside the scope of the FDA's own safety and efficacy assessments of GE animals, and therefore APHIS might need to be a partner in the overall assessment and approval of GE animals. For example, APHIS would need to know if a GE animal might be a "disease vector" that merits quarantine, or whether containment measures for GE animals and their progeny, if required, are sufficient to ensure that livestock markets will not be disrupted.

THE USDA

Since the USDA has not indicated whether or not it intends to use any of the statutory authorities discussed previously to develop a mandatory pre-market approval process for GE animals similar to its process for GE plants, the discussion in this section is necessarily speculative. The threshold question is whether any of these laws provides the USDA with

sufficient and useful legal authority to regulate GE animals and their progeny. The AHPA is discussed first, followed by the other laws implemented by the USDA.

The Animal Health Protection Act

Overall Responsibility and Legal Authority

In theory, the AHPA could provide APHIS with authority to regulate the importation and interstate movement of GE livestock in which the donor, recipient, or vector used to create the GE animal is from a genus known to contain an animal disease or pest, or in which the animal had been altered in a way that made it more or less susceptible to a livestock disease or pest.[37] APHIS could institute a comprehensive permitting system for field trials and the commercial production of GE animals similar to that for GE plants. Under such regulations, APHIS could consider the potential adverse impacts of such animals on other livestock. The AHPA provides APHIS with broad authorities to control movement, including the authority to require testing, impose civil penalties, and take direct actions to prevent the dissemination of livestock diseases and pests.

This approach appears to have limited utility, however, for several reasons. First, the AHPA covers only "livestock," and the scope of that term is not entirely clear. In the pre-AHPA AQ laws, "livestock" was not defined, but it was often construed to cover only traditional farm animals such as cattle, horses, sheep, and swine. The AHPA amendments defined "livestock" to include all "farm-raised" animals, but it did not define "farm." It is thus unclear whether, for example, fish raised in a pond on a farm would now be considered "livestock," or whether an ocean net pen could be considered a "farm" for the purposes of the AHPA.[38] It does seem, however, that animals such as wildlife and pets, as well as the progeny of GE animals, may not be covered by the AHPA.

Second, unlike with GE plants, most genetic engineering of animals does not use animal diseases or pests as donors, recipients, or vectors (NRC 2002a, 39). So, the processes used to genetically transform animals would not make those animals livestock pests for the purpose of AHPA jurisdiction.[39] As a result, probably only those transformations that would themselves change the susceptibility of livestock to diseases or pests or make the animals

37 Very little legislative history exists to indicate the intent of Congress when it passed the AHPA, and none of the documentation mentions GE animals. Congress amended the definition of "move" in the law to include "release into the environment" (7 USC § 8302(12)(E)). In doing so, Congress may have been following the precedent in the Plant Protection Act, where it enacted a similar definition, intended in part to enhance APHIS's ability to regulate GE plants. The similar change might be evidence of a similar Congressional intent in the AHPA to apply the law to GE animals, but there is no discussion in the legislative record to either support or contradict this interpretation.

38 There do not appear to be any restraints on what APHIS may consider a "farm," as long as it comes within the dictionary definition of the term. Recently, APHIS determined that non-GE, hybrid salmon raised in net pens in Maine were "livestock" for the purposes of controlling infectious salmon anemia (USDA 2001).

39 "Pest" is defined in the AHPA to mean any of a list of traditional types of things that cause disease, such as protozoa, bacteria, viruses, and parasites that can directly or indirectly injure, cause damage to, or cause disease in livestock (7 USC § 8301(3)). This is the traditional concept of disease upon which APHIS has used its authority in the past. The law also includes the term "vector," however, of which a disease-carrying mosquito is a good example. If a GE animal, whether livestock or not, were altered or cloned using a viral vector of possible quarantine concern, it could be a candidate for regulation under the AHPA. Currently this approach may be of limited utility. The NRC has stated that the use of viral vectors to induce transgenesis in animals is limited (NRC 2002a, 39).

more likely to harbor pests or pass on diseases would qualify for coverage.[40] Arguably, a transformation event that would have some adverse effect on an animal could also be covered, on the theory that the event itself is a livestock pest. However, it is likely that only a small category of possible genetic transformations would be covered under these interpretations. APHIS might be able to argue that the mere potential of a transformation event to make an animal more susceptible gives the agency jurisdiction to examine the event, but the agency would need some reasonable basis for that assertion.

A third potential limitation is that APHIS can currently regulate only the importation and interstate movement of relevant GE livestock pests. The term "movement" has been newly defined in the AHPA to include "release into the environment" (7 USC § 8302(12)), much in the same manner as in the PPA (§ 7702(9)). It is not clear exactly what "release into the environment" would encompass with regard to livestock. It may be possible to construct an argument that putting GE livestock in a fenced field would constitute release into the environment since, under normal conditions, such animals have been known to get outside fences and have contact with other animals. It is not clear that all such "movements" would be in interstate commerce (as would be required to trigger the AHPA), but the concept may help to justify the need for tracking GE livestock in order to prevent the inadvertent introduction of unintended genes into traditional livestock breed lines and the food, feed, and rendering markets. Nonetheless, the regulatory status of GE livestock that are developed, raised, commercialized, and processed intrastate, as opposed to interstate, is unclear under the AHPA. On face value, those animals would appear to fall outside the scope of the law, except in instances when APHIS declares an extraordinary emergency. If GE livestock could not be moved interstate unless they had complied with certain requirements, this may be adequate incentive for anyone handling or creating such animals to comply with the regulations, as has happened with many GE plants.

Finally, the AHPA would provide APHIS with only limited authority to look at the full range of risks associated with GE animals. The law deals with livestock pests and diseases; it does not address food safety, human health, or environmental risks.[41]

With regard to environmental risks, the AHPA lacks both a broad grant of environmental protection enforcement authority and a specific standard under which any environmental

40 The term "disease" in the AHPA is defined as having "the meaning given the term by the Secretary" of Agriculture (7 USC § 8301(3)). This gives APHIS some discretion as to what constitutes a "disease." But the definition would appear to still have to come within a dictionary definition of the term. *Disease* can be defined broadly to mean any "deviation from the healthy or normal condition of any of the functions or tissues of the body...," including "an alteration in the state of the body or of some of its organs, interrupting or disturbing the performance of the vital functions, and causing or threatening pain or weakness..." (Webster's 1984). Such a definition potentially could allow some GE livestock to be regulated as being "diseased" under the AHPA (e.g., if the overall fitness of the GE animals might be compromised by the technique used to develop them). However, such a definition would certainly not appear to allow APHIS to regulate all GE livestock. For example, if an animal were genetically altered to produce a hormone or pharmaceutical, and the alteration did not impair any organ or function of the animal, it would not appear that APHIS could call the animal "diseased" under the AHPA. Presumably, most people in the business of developing GE animals are doing so in hopes of *enhancing* the health or quality of those animals. Therefore, reliance on a "disease" definition for the regulation of GE animals may be of limited utility.

41 If a disease of human health concern was also a zoonotic disease that affected livestock, it possibly could come under the AHPA. Under this theory, the GE animal would need to be identified as a carrier of a disease that posed a human food safety concern.

review would be assessed and enforced. As a practical matter, APHIS could use its NEPA authority to conduct broad environmental reviews on GE livestock, as is done under the PPA for many GE plants (and as is proposed by the FDA in conjunction with the new animal drug approval process). However, NEPA has the same limitations as a regulatory and enforcement tool for APHIS as were discussed for the FDA.

The AHPA could arguably be used by APHIS to address some environmental concerns associated with GE livestock, since the definition of "moved" in the AHPA includes "release into the environment." However, unlike the PPA and its noxious weed provisions, the AHPA contains no reference to the environment beyond the findings section of the statute and within the definition of "moved." Therefore, environmental factors related to GE livestock that affect diseases or pests of livestock could fall within the regulatory mandate of the AHPA, but environmental impacts related to wildlife or to broader, ecosystems-based concerns would appear to fall outside the regulatory purview of the law.

The AHPA could theoretically be used to develop a tracking and identification system for GE livestock—at least for those livestock that are moved in interstate commerce and subject to AHPA jurisdiction. APHIS could develop a rationale for issuing regulations to require the identification of all GE livestock moved in interstate commerce in much the same manner as it created a program for the FSIS to track swine in interstate commerce. (Swine are required to be identified for the purposes of tracking sulphanomides and other drug residues.[42]) The rationale might be that a GE animal may be a potential disease vector of quarantine concern, or an unapproved GE animal, and if not properly identified and contained, could potentially spread a livestock disease or pest. This type of regulation could help keep many GE livestock out of the food chain and protect animal genetics, when that is desired or appropriate. Tracking the *intra*state movement and sale of GE livestock, however, would remain a challenge.

It is not clear if the progeny of GE animals covered by the AHPA would also be subject to the law. It would depend on the theory of regulation adopted by APHIS, and on whether the progeny exhibited the GE traits and/or carried the GE genetic material of the parent. If the regulations were based on the method of altering the DNA, then it would appear that the progeny would not be covered, since the DNA of the offspring would not have been similarly altered. If the regulations were based on the fact that the animal carried GE genetic material of regulatory concern, then the progeny might be covered, if the progeny had the altered DNA. If the altered trait was not passed to the offspring, then the offspring would not appear to be regulated under this theory. Therefore, no-take animals probably could not be regulated, or cleared for quarantine or environmental safety concerns, under the AHPA. (It is also not clear at what point in the process a determination would be made about whether an animal is a no-take.) In addition, it may be very difficult to identify the progeny of a GE animal once that offspring is separated from its parent. Even if a test is available, it may be too expensive to perform on large numbers of animals. Therefore, the progeny issue could raise difficult enforcement challenges, not only for APHIS, but for the FDA, FSIS, and state regulators as well.

42 In that instance, APHIS promulgated regulations in 9 CFR § 71.19 requiring that swine that are sold, transported, received for transportation, or offered for sale in interstate commerce must be able to be identified so their movements can be traced. This is accomplished by requiring the identification of swine at the first point of sale, movement, or commingling in interstate commerce.

Pre-Market Authority

For GE livestock subject to the AHPA, regulations could require pre-market approval in much the same manner as is currently required for plants. As noted above, however, a number of GE animals may not be covered by the AHPA, and APHIS's authority to look at food safety, human health, and environmental concerns appears to be constrained.

Post-Market Authority

The AHPA appears to contain significant and adequate authority to respond to problems that may arise from any GE livestock that fall under the law. The AHPA also appears to provide ready access to funds for emergency responses to some problems that might arise with GE livestock. Thus, there are no known issues or concerns regarding post-market authority, as long as GE animals remain under permit and are not deregulated as plant pests as is currently done under APHIS's regulations for GE plants.

Clarity, Transparency, and Public Participation

Since APHIS has yet to issue any regulations or guidance concerning the applicability of the AHPA to GE livestock, its policies and procedures are obviously not clear. With respect to transparency, the AHPA contains no limitations on disclosures of safety data, permits, or approvals, other than for confidential business information. APHIS could adopt, under the law, a system of relative transparency with opportunities for public comment, in the same manner it has done for GE plants, with actions and the status of requests posted on web sites and published in the *Federal Register*. Unlike the highly confidential NADA process under the FDCA, the AHPA contains no statutory limitations nor prohibitions on such public notices and comment or other such public participation.

Coordination

Because it remains unclear how comprehensive AHPA coverage would be, coordination would present challenges to APHIS and technology developers. If an AHPA approach is implemented, it seems likely that at least one other agency would have to conduct animal safety and environmental reviews for at least some GE animals and their progeny. APHIS also would need to coordinate with the FSIS to ensure that unapproved animals or animals not intended for the food supply could be kept isolated from the food marketing system and readily identifiable by meat inspectors and processors. APHIS would also likely need to work with the FDA and FSIS to develop, monitor, and enforce an animal identification and tracking system.

The AHPA does not give APHIS authority over human food safety concerns. These issues would remain the responsibility of the FDA. The FSIS could also have a role to play with regard to any GE animals that may deliberately or accidentally enter the nation's meat supply. Also, APHIS would presumably need, in at least some instances, the active participation and consent of federal and state wildlife agencies, including the FWS and NMFS, for some regulatory decisions.

It is difficult to assess whether coordination on all issues related to GE animals can be effectively and legally achieved through administrative options alone.

The FSIS's Meat Inspection Laws

If the FDA takes on the major responsibility for determining the safety of food derived from GE animals, the FSIS's role would largely be limited to enforcing the FDA's decisions about whether GE animals and no-takes can safely enter the food supply. However, to the extent that the FDA decides not to review certain classes of GE animals going into the food supply, the FSIS could also be responsible for determining safety standards for such animals.

A legal issue regarding the FSIS's enforcement of the FDA's decisions could arguably arise. The FSIS lacks, in the FMIA and the PPIA, explicit authority to deem carcasses adulterated based solely on the fact that they have not complied with the FDA's INAD and NADA requirements. The FSIS's adulteration authorities (21 USC §§ 453(g) and 601(m)) and its broad authority to manage the inspection program (§§ 602, 605, 452, and 455) are probably sufficient, however, to support rejecting for slaughter GE animals and no-takes that have not been approved by the FDA. Though not clearly adulterated under the FMIA or PPIA, food derived from such unapproved animals would violate the FDCA, and the FDA would have the authority to keep the animals out of the food supply. Under those circumstances, courts are unlikely to require that the FSIS pass them through the slaughter process.

The more significant issue is the lack of an identification and tracking system for animals coming into FSIS-inspected slaughter plants. GE animals and no-takes may not be visibly different than conventional animals. If a researcher or commercial operator circumvented FDA and FSIS review procedures, either accidentally or on purpose, and offered a GE or no-take animal for slaughter, the FSIS would have no way to distinguish that animal from a non-GE animal. Thus the agency would be unable to enforce FDA and FSIS requirements that the safety of these animals be reviewed and approved in advance.

The Plant Protection Act

Several issues arise with the potential application of the Plant Protection Act to GE animals. The first is a question of scope. Virtually all grazing animals (conventional and transgenic) could theoretically be considered plant pests under the PPA, since they feed on plants. There is nothing to indicate that Congress intended the PPA to be interpreted so broadly, however, and such an interpretation could be open to challenge. Even if the interpretation could be sustained, APHIS's ability to consider the full range of food safety, animal health and welfare, and environmental risks under the PPA is constrained for animals no less than it is for plants, as discussed in Chapter 2. In fact, the PPA's environmental risk management authority is more limited for animals than for plants. The PPA defined "noxious weed" to include plants that could harm the environment or natural resources, but there is no similar authority or definition that would apply to organisms other than plants that are weeds.

The Animal Damage Control Act

As with other USDA laws, the applicability of the Animal Damage Control Act to GE animals raises a threshold issue of scope. As recently amended, the ADCA authorizes APHIS to implement a "wildlife services program concerning injurious animal species" and take "any action necessary" (7 USC § 426). This broad grant of authority, however, is limited by the subsequent provisions, which direct APHIS to carry out the program "in a manner consistent with all of the wildlife services authorities" previously in effect (§ 426). The law

does not define "injurious animal species." Historically, however, the program has been directed at controlling wild mammals and birds that injure agriculture or that are reservoirs of zoonotic diseases.[43] The law permits APHIS to enter into cooperative agreements with states to eradicate and control troublesome mammals and birds. The previous law enumerated several specific species of concern.[44]

In theory, APHIS could find that a transgenic animal was "injurious" if it harmed agriculture, among other things.[45] It is questionable, however, whether the agency could use this law to create a comprehensive regulatory system for experimental releases and commercial production of GE livestock. Such a program would appear go well beyond, and could therefore be unlawfully inconsistent with, existing cooperative agreements to eradicate and control nuisance wildlife. The "control" envisioned in the ACDA means controlling population levels through eradication programs. Such programs would appear to have little applicability to domesticated GE livestock. However, such a program could provide authority for APHIS to respond in the event that a GE animal escaped or unwanted gene flow moved into a wild or domesticated population.

The Animal Welfare Act

The scope of the Animal Welfare Act is unclear, given ambiguity in the law's definitions of "research animals" and "livestock." While the law would not cover livestock grown for food purposes, it is unclear whether a herd of cattle producing pharmaceutical products would be considered "livestock" or "research animals" for the purposes of the law. At a minimum, the authorities of the law may be useful in bringing certain research establishments into a system for tracking experimental GE animals that should not be allowed into the food supply.

Approaches to Resolving the Issues and Concerns

This section lays out a variety of options for resolving the issues and concerns regarding the existing regulatory system that were raised in the previous section, should policy makers decide that improvements are needed. The FDA is discussed first, then the USDA.

THE FDA

The issues identified previously concern the scope of the FDA's authority over GE animals, its authority to require a mandatory pre-market approval, and its authority to consider animal health, human health, and environmental issues. Policy makers will need to decide what role the FDA will ultimately play in the regulation of GE animals, including whether the agency will be involved beyond ensuring food safety through its post-market enforce-

43 The more detailed language in the earlier law provided APHIS with authority to conduct "investigations, experiments, and tests" to "determine, demonstrate, and promulgate the best methods of eradication, suppression, or bringing under control...animals injurious to agriculture, horticulture, forestry, animal husbandry, wild game animals, fur-bearing animals, and birds..." (7 USC § 426 (repealed)).

44 Specifically mentioned were mountain lions, wolves, coyotes, bobcats, prairie dogs, gophers, ground squirrels, jack rabbits, and brown tree snakes.

45 APHIS would presumably need to show that the animal was, in fact, injurious, and was not just potentially injurious.

ment powers. The following options set out some of the alternatives for defining the FDA's role and giving it authority to address the issues raised, if policy makers decide that such a course is appropriate.

The first option considers a food-safety-only approach under the FDA's general food safety authority. The second option addresses the new animal drug approval approach, and outlines several administrative reforms that the agency could undertake, if this route is pursued, to address some of the issues raised. The third option is an "overlay" approach to making legislative changes to the new animal drug approval provisions of the FDCA, which would resolve some of the issues relating to environmental authority, but not those regarding public participation and transparency. The final option is a proposal for amending the new animal drug provisions of the FDCA in a more comprehensive way, to address all of the perceived limitations of the existing system. The latter three options are not mutually exclusive.

Food-Safety-Only Approach

The FDA could clarify its regulatory approach to GE animals by indicating that it intends only to consider the food safety aspects of foods derived from GE animals. If the agency chooses this approach, it would be unlikely to adopt a mandatory pre-market approval system, instead finding that added substances would presumed to be GRAS if they were substantially similar to substances already present in the food supply. While this approach could expedite product development and reduce review costs for both developers and the FDA, the lack of a mandatory pre-market approval would likely raise the same kinds of concerns that have been expressed about foods derived from GE crops and discussed in Chapter 3. In addition, under this approach, the FDA would have no authority to consider animal safety or environmental risks associated with GE animals.

Administrative Reforms for the NADA Approach

If the FDA chooses to proceed with using its new animal drug authority for GE animals, the agency could be encouraged to undertake the following administrative activities in order to improve its regulatory system:

- develop guidances and criteria governing the safety of food resulting from GE animals;
- develop guidances and criteria assuring that no unreasonable adverse impacts to the environment occur as a result of the development and marketing of GE animals;
- develop a specific enforcement/inspection program for GE animals, beginning with the INAD process and including commercialization;
- develop guidelines for animal identification and tracking, as deemed necessary;
- develop guidelines for the handling and disposal of animals (or animal carcasses) not intended for the food or feed supply;
- develop guidelines for animals that meet the research exemption under the NADA, and for when animals require an INAD and when they require an NADA;
- define no-takes and develop guidelines for their disposition and handling;

- develop GLP and GMP standards that are relevant and appropriate for GE animals;
- develop guidances or regulations regarding the FDA's authority to impose environmental mitigations and the types of mitigations appropriate in given circumstances; and
- consider mechanisms for informally and formally coordinating decision-making among the federal agencies that possess authority and expertise regarding investigational use, pre-market review, and post-market enforcement related to GE animals.

Animal Drug "Overlay" for the Regulation of GE Animals

From time to time in the course of its oversight of food and drug regulation, Congress has amended the FDCA by augmenting or "overlaying" the existing regulatory system, not in an effort to revise that authority but rather to add authority—to provide an additional layer of public health protection or address a deficiency in the existing authority.

An example is the Infant Formula Act of 1980 (IFA; 21 USC § 350a). Prior to 1980, the FDA for 40 years had regulated infant formulas as "special dietary foods." As such, infant formulas were subject to the same safety standards as other foods. In 1980, a large infant formula manufacturer failed to include chloride in several batches of formula. This failure resulted in severe health reactions in a significant number of infants (including metabolic alkalosis or high blood pH, characterized by poor appetites and failure to thrive). The infants recovered after being taken off the formula and given chloride supplements (CDC 1999). In response to this crisis, Congress amended the FDCA with the passage of the Infant Formula Act. The IFA contains a series of protective measures involving nutrient requirements, pre-market analysis for nutritional quality, pre-market notification, quality-control practices, and agency records access designed to ensure that a nutritionally deficient formula will never again be marketed. In passing the IFA, Congress did not add any new safety authority to the FDA's general food adulteration provisions, nor did it expand upon the need for infant formula food ingredients to be either GRAS or meet the food additive provisions of 21 USC § 348. The IFA, rather, was a nutrition-based "add-on" initiative designed to provide extra levels of assurance regarding the nutritional quality of formulas.

Examples of similar overlay efforts in response to perceived public need include the Orphan Drug Act (21 USC §§ 360cc-dd) and the pediatric provisions of the FDA Modernization Act (21 USC § 355A(b)). In these cases, Congress recognized that the existing new drug approval systems did not provide meaningful incentive for manufacturers to investigate and bring to market drugs for rare diseases and drugs specifically shown to be safe and effective for use in children. Both amendments created a series of incentives for manufacturers to develop drugs for such indications. In each case, the primary "carrot" provided was market exclusivity, while the fundamental standards for showing safety and establishing effectiveness for such drugs were left unchanged.

In the context of GE animals, consideration of such an overlay approach would have to begin with the conclusion that regulating such animals under the animal drug provisions of the FDCA is appropriate. This conclusion recognizes that, under the new animal drug rubric, the FDA has the authority to ensure that human food derived from GE animals is safe and that the drug (or genetic modification) does not harm the animal. Because the animal drug rubric is not tailored to address environmental concerns resulting from genetic modifications that will persist from generation to generation, however, there is no

clearly articulated standard for assessing the risk that such exposure presents to people and to animals. An overlay amendment could expressly vest the FDA with such "add-on" environmental assessment authority and provide the standard and governing criteria to be employed in making such evaluations. The overlay could also expressly authorize the agency to impose monitoring conditions for environmental effects. These overlay changes would not alter the agency's current practices in regulating conventional new animal drugs or the extensive precedent accumulated regarding the demonstration of safety and effectiveness. Other possible candidate overlays include standards for animal welfare during product testing and more fundamental government oversight of nonclinical, basic animal research preceding the INAD phase of inquiry. An overlay provision could also contribute to greater transparency by providing for mandatory advisory panel review of the environmental impacts of GE animals and requiring that advisory committee recommendations be made publicly available.[46]

Even if an overlay approach were to result in meaningful adjuncts to the FDA's regulatory authority over animals, the approach followed by the FDA would still, to an extent, represent an ad hoc extension of existing regimes and not reflect a unified federal strategy. Lack of transparency and public participation could remain problematic deficiencies. Public confidence, however, in the FDA's decision making with regard to the food products of GE animals could remain high.

Legislative Amendment to Section 512 and Related Provisions of the FDCA

Figure 4.3 presents another possible legislative approach. It is clearly not an overlay, but rather would amend the new animal drug provisions of the FDCA (FDCA § 512; 21 USC § 630(b)) in order to correct most, if not all, of their perceived shortcomings with regard to using these authorities to regulate GE animals.

THE USDA

Several options exist for employing the various USDA authorities to regulate GE animals. The AHPA and PPA are discussed first below, followed by the meat inspection laws and the Animal Welfare Act.

The AHPA and PPA

This section describes possible administrative reforms and legislative changes for addressing the issues and concerns raised previously regarding use of the AHPA and the PPA to regulate GE animals. These reforms make the assumption that APHIS would use AHPA and PPA authorities to address animal health and environmental issues, while the FDA would address food safety and, potentially, under the new animal drug approval process, the safety and efficacy of the particular transformation events themselves.

46 Apart from overlay considerations, legislative initiatives might also be considered to (1) ensure adequate resources to administer the necessary course of regulation and, perhaps, (2) to foster education, throughout industry and the consuming public, regarding the application of the technology and the contours of government regulation.

Figure 4.3 Possible Legislative Amendment to the FDCA

Definitions – First, the definitions section of the law could be amended. Specifically, the term "animal drug" could be amended to make it explicit that the term includes "GE animals." The term "GE animal" could be defined to include not only the initial generation of genetically altered animals but also their offspring and subsequent generations that inherit the genetic alteration. The term "no-take animal" could also be defined.

Enforcement – The food adulteration provisions of the FDCA could be amended to deem food adulterated, and thus unlawful, if the food is, or if it bears or contains, any product of a GE animal or a no-take animal that has not been approved for food use under Section 512. These provisions would provide the legal basis for FDA enforcement of the requirement that food from GE and no-take animals must be evaluated and approved as safe by the FDA before it is allowed to enter the food supply.

Special Provisions for Pre-Market Review and Approval of GE Animals – A new subsection (q) could then be added to Section 512 of the FDCA to provide the FDA with new authorities and directions regarding the regulation of GE animals as animal drugs. This new subsection is envisioned to have 13 parts.

- **Application to Subsequent Generations.** Section (q)(1) would make it explicit that, in administering Section 512 with respect to GE animals, the FDA must consider the effects on health and the environment of both the initial generation of GE animals and all subsequent generations that inherit the genetic alteration.
- **FDA Exemption Authority.** Section (q)(2) would provide the FDA with authority to exempt certain GE animals from the regulatory requirements of Section 512 if the animals are intended solely for scientific research or other noncommercial purposes, but only if the animals are not intended or expected to enter the food supply or be released into the environment. This new subsection also would give the FDA authority to impose containment requirements or other controls on exempt animals, as needed to protect food safety or the environment. This section is intended to enable the FDA and the biotechnology industry to avoid the regulatory burdens of Section 512 with respect to noncommercial uses of GE animals that do not affect the food supply or the environment.
- **Enforcement Against Subsequent Generations.** Section (q)(3) would make explicit that the FDA is able to enforce the requirements of Section 512 against not only the initial generation of GE animals but against the offspring and all subsequent generations that inherit the genetic alteration.
- **Review of Labeling Requirements.** Section (q)(4) would direct the FDA to review the labeling requirements applicable to animal drugs under the FDCA and in the FDA's regulations and would give the agency authority to exempt GE animals from any labeling requirements that are not applicable to GE animals or are unnecessary to protect health or the environment. This provision is needed to adapt current animal drug labeling requirements, such as the requirement that the labeling of animal drugs provide adequate directions for use, to the way in which GE animals will be used.
- **Regulation of Investigations.** Section (q)(5) would establish requirements and procedures for the FDA's regulation of investigations involving GE animals. It would establish a threshold for FDA oversight of the production of animals for research outside a contained setting or for investigations intended to support FDA approval of a product. This section would assume that the FDA's current investigational new animal drug regulations will apply to GE animals, but it would direct the FDA to amend those regulations as needed to address GE animals and to require, with respect to investigations involving GE animals, that:

Figure 4.3 Possible Legislative Amendment to the FDCA (...continued)

- animal welfare is addressed, consistent with the standards and procedures under the Animal Welfare Act;
- animal tracking and identification systems are in place, as provided in a new Section 512(q)(6);
- containment or other measures are in place to ensure that the investigation will cause no unreasonable adverse environmental impact;
- any food products produced by animals in the investigation are not used for human or animal consumption unless the FDA grants affirmative approval;
- the investigational notice and supporting data and information are put on public display, except to the extent the sponsor demonstrates that some or all of the material is exempt from disclosure as trade secret or confidential commercial information;
- if the sponsor seeks approval for food or feed use of products produced during the investigation, or there is a reasonable likelihood the animals will be released or escape into the environment, the FDA would: (1) put the relevant health and environmental data on public display, (ii) provide an opportunity for public comment on the notice, and (iii) provide a clear public explanation for its decisions in response to the notice.

- **Animal Identification and Tracking.** Section 512(q)(6) would require that GE animals and no-takes that are involved in FDA-regulated investigations be separated from other animals and subject to a system of individual identification and tracking measures, as prescribed by the FDA. This system would have to be sufficient to maintain a complete inventory of such animals and their ultimate disposition and allow inspectors to determine whether individual investigational animals have been approved for food use or release into the environment. These controls would remain in place until the animals are approved by the FDA for commercial use. The purpose of this section is to ensure demonstrable control over investigational GE animals and associated no-takes until the FDA has made affirmative decisions about their safety for health and the environment.
- **Authority to Regulate Environmental Impacts.** Section 512(q)(7) would make explicit the FDA's authority to regulate the environmental impacts of GE animals. It would require that applications for approval of a GE animal contain data and information demonstrating that the intended and reasonably foreseeable commercial use of the animal will cause no unreasonable adverse environmental impact. It would also prohibit the FDA from approving a GE animal unless it finds that the data and information in the application are sufficient for this purpose and that commercial use of the GE animal will cause no unreasonable adverse environmental impact.
- **Consultation With Other Agencies.** Section 512(q)(8) would require the FDA to consult with other federal agencies on the potential environmental impacts of GE animals at both the investigational and final approval stages. It would specifically prescribe consultation with the FWS and NMFS on GE fish, including a requirement for a written report on whether the investigation or application meets the standard of "no unreasonable adverse environmental impact" with respect to fisheries, wildlife, and natural ecosystems. The FDA would have to consider the opinions received from the consulting agencies and document the basis for reaching any conclusions that conflict with those opinions. The purpose of this consultation requirement is to help ensure that the FDA can make well-informed, scientifically sound decisions about the potential environmental impacts of GE animals.
- **Transparency and Public Participation.** Section 512(q)(9) would provide for public participation in the FDA's consideration of applications for commercial approval of GE animals. It would require the FDA to place applications on public display and provide a reasonable opportunity for public comment, which the agency would be required to consider and respond to in acting on the application. The FDA

Figure 4.3 Possible Legislative Amendment to the FDCA (...continued)

could withhold from public disclosure trade secret and confidential commercial information other than data and information relating to the safety of the GE animal for health and the environment.

- **Post-Approval Conditions and Monitoring.** Section 512(q)(10) would provide the FDA with explicit, discretionary authority to (1) impose conditions on the commercial use of an approved GE animal, as needed to avoid unreasonable adverse environmental impacts, and (2) require the applicant to conduct post-approval monitoring and data collection, as needed to detect any significant unanticipated consequences for health or the environment that might result from the commercial use of the animal.
- **Revocation of Approval.** Section 512(q)(11) would address the conditions and procedures under which the FDA may revoke the approval of a GE animal. In addition to the grounds applicable generally to revoking approval of animal drugs, this provision would provide for the revocation of approval of a GE animal if (1) the FDA determines that any of the post-approval conditions or requirements imposed under Section 512 (q)(10) have not been observed, or (2) the FDA, based on new evidence or analysis, no longer concludes that the GE animal or its progeny will cause no unreasonable adverse environmental impact. This provision would also simplify the process for revoking the approval of a GE animal by substituting an informal hearing for the formal hearing applicable generally to animal drugs. It would not alter the right to judicial review of revocation decisions.
- **Recall Authority.** Section 512(q)(12) would give the FDA authority to order the recall of a GE animal and its progeny following a revocation of approval of the animal or if necessary to prevent an unreasonable risk of harm to health or the environment. The FDA would have to provide the sponsor with reasonable notice and an opportunity for an informal hearing before issuing the recall order.
- **Miscellaneous Implementing Provisions.** Section 512(q)(13) would contain several provisions intended to promote transparency and public understanding concerning the administration of Section 512 with respect to GE animals, including instructions to the FDA to:
  - revise its regulations applicable generally to animal drugs to address issues posed by GE animals;
  - issue regulations or guidance, following an opportunity for public comment, describing (1) the data and information required to be submitted with investigational notices and approval applications in general and in specific cases, (2) how the FDA will evaluate the potential environmental impacts of GE animals, and (3) how the FDA will use its authority to impose conditions on use and other requirements to avoid potential adverse environmental impacts and require post-approval monitoring and data collection;
  - place approved GE animal applications on public display and make them readily available to the public through the internet;
  - develop and make public, with opportunity for public comment, a comprehensive GE animal inspection and enforcement program, covering both investigations and commercial use; and
  - formalize and make public, following an opportunity for public comment, APHIS's relationships and procedures with other agencies regarding the review of investigational notices and approval applications and the establishment of cooperative enforcement programs.

Administrative Changes

While all GE animals cannot be regulated under the AHPA or the PPA as they are written, APHIS could possibly regulate some GE livestock for disease and pest concerns under these laws. A threshold question is whether either law can be used to cover *enough* ani-

mals of interest to warrant the development of an administrative framework. The approach described here assumes that the AHPA and PPA can be reasonably construed to cover most, if not all, GE animals of interest. If the scope of these laws proves to be too limited, Congress would need to provide APHIS with additional authority, as discussed later.

APHIS could set up a program under the auspices of either the AHPA or the PPA to regulate GE livestock at least in a manner similar to its current regulation of GE plants under 7 CFR Part 340. New AHPA or PPA regulations could include the following elements:

- Notification or permits could be required for the movement or release into the environment of AHPA- or PPA-covered GE animals, including the release of such animals into adequately secure enclosures, until it can be concluded that they do not pose significant risks to livestock or plants.
- APHIS could require a general or specific permit for the marketing and commercialization of any GE animal subject to the AHPA or PPA, including GE livestock and perhaps other GE animals whose transformation techniques or characteristics pose disease or pest risks to livestock or plants in general.
- Any conclusion or risk concerning an AHPA-regulated GE animal could be reevaluated if reliable new information or evidence of a new risk is obtained.
- Failure to abide by any permit condition or failure to submit requested information could be grounds for revoking any permit regarding the movement, release into the environment, or commercialization of a GE animal and could be the basis for revoking any registration or license required for doing research on GE animals.
- Methods could be developed (e.g., memoranda of understanding) for sharing information and coordinating decision making among the federal and state agencies with authority over GE animals.
- APHIS could develop and require specific GE animal identification, tracking, and monitoring activities for those GE animals falling under the authority of the AHPA or PPA.
- APHIS could define what GE animal progeny, including no-takes, fall under AHPA or PPA authority and develop and require, as necessary, approval, identification, tracking, and monitoring for these animals.

The regulations would not include a provision by which any GE animal is deregulated or otherwise not subject to the AHPA or PPA. This would allow APHIS to exercise post-market controls on regulated GE animals.

Legislative Amendments

If it is deemed desirable to make APHIS the primary agency for the assessment of environmental risks associated with GE animals and to require developers to obtain pre-release (into the environment) approval from APHIS for all GE animals, Congress could amend the AHPA to give APHIS explicit authority to regulate GE animals. Such an amendment would avoid the ambiguities that would arise from relying on the definitions in the AHPA, PPA, and ADCA to assert authority over GE livestock and GE animals in general. Legislation could also clarify the regulatory status of the progeny of GE animals—both offspring con-

taining GE traits and no-takes. The law could define a process by which the safety of these animals could be assessed and through which GE animal progeny could be released into the environment or commercialized. (For example, is any review necessary? Is a complete case-by-case pre-market review necessary? Or is some expedited review process appropriate?)

As discussed previously, the AHPA does not give APHIS the same authority to regulate the potential environmental risks of GE animals as the PPA does to regulate GE plants. Many of the discrepancies between the two laws could be eliminated by changing a few provisions in the AHPA to mirror similar provisions in the PPA. For example, "noxious weed" is defined in the PPA to include "any plant or plant product that can directly or indirectly injure or cause damage to...the natural resources of the United States...or the environment" (7 USC § 7702). There is no comparable provision in the AHPA. The AHPA could be amended to include such a concept as part of a definition of "animal pest," so that APHIS could take action under the AHPA against any animal that could directly or indirectly injure or cause damage to the natural resources of the United States or the environment. The AHPA would need to explicitly identify "environmental risks" as one of the review criteria for GE animals, to clarify that all GE animals fall under the purview of the AHPA. Legislation could also clarify what risks to the natural resources of the United States and the environment are clearly covered under the AHPA.

The AHPA could be amended to give APHIS clear authority to set up a mandatory pre-market or pre-"movement" (pre-release) approval system for all GE animals. The law could authorize APHIS to require persons who want to conduct research on GE animals to register with APHIS; it could also give the agency clear authority to promulgate regulations concerning the steps that must be taken before a GE animal could be released into the environment or marketed. Such steps could include data submission, tracking, and monitoring, as necessary for APHIS to identify the potential livestock disease and pest risks associated with a GE animal and the animal's potential to have "an unreasonable adverse effect on the natural resources of the United States or the environment." Similar pre-release or pre-market approval authorities could be conferred to APHIS to ensure that GE animals are contained and handled, as appropriate, to avoid risks to the food or feed supply and the livestock market.

APHIS could also be granted clear authority to prescribe requirements for containment and to take action under the AHPA if the requirements are not followed. Enforcement actions could include assessing civil and criminal penalties, as well as remedial actions to abate any possible livestock disease or pest risks, risks to the natural resources of the United States, or unreasonable environmental risks. APHIS could also be given clear authority to promptly mitigate animal health or environmental damage caused by GE animals, without the requirement to invoke its extraordinary emergency authorities. APHIS should have sufficient enforcement tools available if all of the approval, enforcement, and monitoring mechanisms associated with the AHPA for livestock disease and pest risks were available for use with regard to all GE animals and their progeny (including no-takes).

Finally, to ensure that APHIS adequately consults with other regulatory agencies, the AHPA could be amended to require interagency consultations with the FDA and FSIS on food-safety-related concerns, particularly if APHIS is expected to oversee GE animal identification and tracking. APHIS could also be required to consult, as appropriate, with the FWS, NMFS, and the EPA on environmental concerns regarding GE animals. In addition,

APHIS could coordinate with state regulators, if the states are expected to play a role in monitoring and enforcement.

The Meat Inspection Laws

If policy makers want the FSIS to be able to provide reasonable assurance that unapproved GE and no-take animals are being excluded from the food supply at the point of slaughter, some form of animal identification system is needed so that inspectors can readily identify animals as GE, research or no-take animals and determine their approval status. The technical capability to implement animal ID systems exists and is being used by many producers for commercial reasons. The policy issues involved in mandating animal identification include (1) under what authority and agency it could and should be mandated and (2) what form the system should take.

The FDA's and FSIS's broad authority to issue regulations for the efficient implementation of the FDCA, FMIA, and PPIA may be sufficient to support an animal ID requirement. Since such regulations are on stronger footing legally if they can be justified as needed to implement a specific adulteration or misbranding provision, the FDA may have stronger legal authority (using the new animal drug provisions) than the FSIS. Animal identification could serve broader purposes, however, such as to conduct traceback investigations following foodborne illness outbreaks or to support country-of-origin or other labeling requirements. It might thus be advisable to consider animal ID in this broader context and pursue it as a joint program of the FDA and FSIS. These issues would need to be coordinated with the recently announced plan to establish a tracking system to monitor bovine spongiform encephalopathy (also known as "mad cow disease") (USDA 2003).

Regarding the form of the system, the broadest policy issue is whether it should be comprehensive (e.g., embrace all cattle or hogs) or limited to GE animals and no-takes. The latter approach would be less costly. On the other hand, it would be less likely to address the problem of researchers or others unintentionally or intentionally circumventing the approval system for GE and no-take animals.

The Animal Welfare Act

While it is clear that research animals, in general, are to be protected under the Animal Welfare Act, it is less clear how GE livestock that are also research animals would be viewed under this law. Presumably, GE animals that are ultimately approved for release into the food supply (or other agricultural uses such as wool production) would qualify for exemptions from the AWA because they are farm animals. Conversely, GE livestock that are used to manufacture pharmaceuticals or industrial chemicals and are not intended for human food would appear to be covered under the AWA. If these observations hold true, the regulatory status of the different "uses" of GE animals could possibly be addressed through new regulations under the AWA. However, if the intent is to cover all GE animals under the AWA, then legislation would more than likely be needed to clarify the standing of GE animals under the law. Also, if it is desirable to require that all GE animal researchers register their facilities under the AWA for the purpose of assisting in the identification and tracking of GE animals (to ensure adequate containment for health, safety, and marketing reasons), legislation would more than likely be necessary to achieve such an outcome.

Regulatory Coordination for Genetically Engineered Crops: A "Single-Door" Approach

While the previous chapters each focused on the regulatory systems of one or two federal agencies, this chapter is centered on the issue of coordination among the various agencies. In particular, it addresses possible approaches for improving coordination among the U.S. Department of Agriculture (USDA), the Food and Drug Administration (FDA), and the Environmental Protection Agency (EPA)—the three agencies with primary responsibility for genetically engineered (GE) plants, animals, and products under the 1986 Coordinated Framework (OSTP 1986). One possible approach for coordinating the regulatory systems governing GE plants is described in detail.

At present, the Coordinated Framework is expected to serve as a regulatory safety net under which all plant-based products are subject to pre-market oversight by at least one federal agency, and sometimes by two or three agencies (OSTP 1986). For example, for plants that produce pesticidal substances (called "plant-incorporated protectants," or PIPs), three agencies are typically involved.

1. The USDA's Animal and Plant Health Inspection Service (APHIS) reviews plants for their potential effects on agriculture and the environment under the Federal Plant Pest Act (formerly 7 USC § 150aa et seq.), now subsumed by the Plant Protection Act (PPA; 7 USC § 7701 et seq.), and also under the National Environmental Policy Act (NEPA; 42 USC § 4321 et seq.).

2. The EPA reviews the potential effects on human health and the environment of pesticidal substances produced by plants, under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA; 7 USC § 136 et seq.) and the pesticide residue provisions of the federal Food, Drug, and Cosmetic Act (FDCA; 21 USC § 346a).

3. The FDA reviews the food and feed safety and nutritional aspects of whole foods, and any other nonpesticidal substances that might be added to plants through genetic alteration, under the food safety provisions of the FDCA (21 USC § 301 et seq.).

While agencies have worked to increase cooperation and coordination, issues remain. In particular, the system can present challenges for small companies and public researchers, who often face multi-agency reviews with little or no comprehensive guidance on who must be talked to and when. Also, the interested public is left largely in the dark about how any given GE product is proceeding through the regulatory review process, particularly given that some agency guidance is unclear or lacking and some key decisions are made via informal, private consultations. Due to this lack of transparency, it is nearly impossible to track a GE product from the initial phases of regulation (e.g., a field trial) through to commercialization (e.g., a GE food set to enter the food supply) via the information provided by the agencies on their respective web sites. Product characterizations and the timing and substance of posted data vary widely. And there is no single, authoritative source of information about specific products undergoing regulatory review. Also, technology developers often claim confidenti-

ality for large portions of submissions, making it difficult for third parties to make independent assessments, particularly prior to commercialization (NRC 2000, 177-178; 2002b, 178).

The regulatory system can also appear to be unpredictable. Many procedures for product review and safety assessment are not spelled out in formal regulations, policies, or guidelines. Given the diversity of products under development and the rapidly advancing state of the science, the agencies have elected to develop their review procedures largely through case-by-case assessments of individual submissions. For those not directly involved in the process, attempting to determine what was done and why, or whether a similar process will be followed in the future, can be difficult. In the case of APHIS and the FDA, it is not clear how newer products that incorporate pharmaceuticals and vaccines into crops are being reviewed. Moreover, it is not clear that like reviews are conducted in the same manner or with comparable rigor by different agencies (e.g., ecological risk assessments by APHIS and the EPA (NRC 2000, 165-166, 170-171; 2002b, 178) and allergenicity assessments by the FDA and the EPA complement one another (NRC 2000, 168-169)).

In general, the agencies appear to have avoided overlapping reviews and responsibilities through understandings reached in the development of the Framework and through interagency memoranda of understanding (USDA and EPA, no date). The substance of these understandings is not readily available to the public, however, and the possibility of redundancies exists, particularly in the review of PIPs by the EPA and APHIS.

This chapter reviews options for achieving greater coordination among the agencies that regulate GE plants and GE plant products, should policy makers decide that such change is needed.

General Options for Improving Coordination

The pros and cons of two general categories of coordination options are reviewed in this section: formal coordination solutions and minimal change administrative reforms.

Formal coordination solutions would include the establishment of a "super-coordination" office within the executive branch at a very high level, in order to ensure sufficient political muscle to "enforce" greater coordination. Such authority might be placed in the Office of Science and Technology Policy (OSTP), the Council on Environmental Quality (CEQ) or the Domestic Policy Council.[1] A second version of this option would be to designate a single lead agency with responsibility for affirmatively coordinating the reviews conducted by each of the agencies involved (e.g., APHIS for all GE plants and the FDA's Center for Veterinary Medicine for all GE animals). This lead agency could be fixed for all products or could vary depending on the nature of the product involved. Either of these approaches would strengthen coordination, reduce or eliminate redundancies, improve predictability, and provide a single point of contact and source of information regarding reviews and clearances. New legislation would not be required.

1 This approach was taken with the establishment of the Biotechnology Science Coordinating Committee (BSCC) within the OSTP (OSTP 1986). The BSCC coordinated initial federal agency efforts to implement the Coordinated Framework. The BSCC is no longer an active entity.

Some countries have long-standing, formal, multi-agency review processes for pesticides, which may provide lessons for such a coordination process.[2] Other countries have established new offices to coordinate the reviews of agencies that have long-standing expertise in areas such as food safety and the environment.[3]

Neither of the formal coordination approaches discussed above would necessarily increase the comprehensiveness of the safety assessment process nor provide additional resources. If not handled properly, these options could introduce delays into some aspects of the review process by increasing the number of transactions among government agencies. A high-level coordination office could find it cumbersome to synchronize the hundreds of routine reviews that would be required. Finally, any option that relied on coordination under the leadership of an office generally regarded as subject to significant, direct political influence might not be perceived as sufficiently independent or scientifically credible.

A variety of administrative reforms could be implemented with relatively modest effort and disruption to existing programs at the EPA, APHIS, and the FDA. These reforms could address many of the problems noted with respect to comprehensiveness, predictability, and redundancy (as well as user-friendliness for small companies and public researchers), without the need for legislative action. On their own, these relatively modest reforms would probably not be enough to improve coordination significantly, however.

A "Single-Door" Coordination Proposal

Should more significant change be desired, elements of the formal coordination and administrative reform approaches described above could be combined into a sort of hybrid proposal. This section describes one such hybrid—a single-door approach—that seeks to significantly improve coordination among the agencies for plant-based products. It is certainly not the only such proposal that could be devised, but it is offered here as a starting point for discussion.

This hybrid proposal envisions the creation of a single "door" or interagency Coordinating Committee through which each transgenic plant and plant product would enter the multi-agency review process. The Coordinating Committee would designate a Lead Agency with the necessary expertise and authority to review each specific category of plant-based products. The various clearances and interactions required for any given product would, as now, be tailored to the nature of the plant and its intended use and to the unique regulatory responsibilities of the individual agencies involved. The Coordinating Committee would track the review process from start to finish and ensure that the necessary clearances were obtained from the appropriate agencies at the appropriate points in the process.

2 For example, the German system of environmental management regulates pesticides and other hazardous chemicals through a multi-agency review process (UBA, no date). Australia has developed a central, federal Office of the Gene Technology Regulator, which provides a coordination function similar to that discussed in this chapter. (See http://www.ogtr.gov.au/about/index.htm for more information.)

3 The new European Food Safety Authority, legally established in 2002, seeks to operate a "one door-one key" procedure for all food safety approvals, including those involving GE foods. (See http://www.efsa.eu.int/ for more information.)

Under this proposal, the Coordinating Committee would serve as the primary source of information concerning the regulatory status of each product, tracking the process throughout for the agencies, developers, and the public. The tracking process would be clearly laid out in one place and readily accessible to the public on the internet. The Committee would provide easy access to up-to-date information on key decision points for each submission, cross-referenced by plant, expression product, trait, developer, agency, and/or other appropriate parameters.

The remainder of this chapter describes several key aspects of this hybrid proposal in more detail, including the scoping process and how the Coordinating Committee and Lead Agencies would function.

THE SCOPING PROCESS

As envisioned in this proposal, scoping would be an interagency process used to determine (1) the range of issues to be addressed with respect to a particular application for pre-market clearance of a GE product and (2) the appropriate agencies with jurisdiction over those issues. The scoping process could work as follows:

1. **Pre-Application Submission**
   The applicant would submit a summary of the pertinent facts about the product, its intended use(s), and why the applicant believes it will be able to make a case for the safety and commercialization of the product.[4] This could be done prior to the completion of all the final studies. If done at that stage, however, the submission would lay out which studies and data will be included in the application. Preferably the summary would be submitted to the Coordinating Committee, although whichever agency receives the summary would provide it to the Coordinating Committee to ensure a coordinated approach to further action.

2. **Pre-Application Review (Major Product)**
   a. Products would fall into this category at the request of the applicant or when triggered by the concerns of agencies (see #3 below).

   b. Under the aegis of the Coordinating Committee, a standing committee made up of one representative from each of the three principal agencies with jurisdiction over GE products (APHIS, the EPA, and the FDA) would review the summary submitted by the applicant and determine whether any other agencies (e.g., in the Department of Interior) need to be involved.

   c. The Coordinating Committee would arrange for a meeting of the appropriate agencies to identify the relevant scientific and regulatory issues and the appropriate regulatory pathway for handling the application.

   d. The Coordinating Committee, within a predetermined period of time (weeks or months) after the receipt of the summary, would provide the applicant with a meeting opportunity to discuss the matter with representatives of the agencies involved. At the meeting, the agencies would communicate any potential roadblocks and

4 Potential paperwork reduction issues would have to be addressed with the Office of Management and Budget prior to the adoption of any coordination proposal.

concerns, and the applicant could learn whether there might be a need for further testing or more intensive examination of the product. The applicant could also use the meeting to clarify issues associated with the application and/or provide additional information.

e. Following the meeting with the applicant, or if the applicant declines the meeting opportunity, the Coordinating Committee would provide the applicant with a letter with collated comments from each agency, including perhaps a cover letter from the coordinating agency and individual comments on letterhead from each individual agency. The comments could address, among other things, the appropriate regulatory pathway for the application and possible data requirements.

3. **Routine/Noncontroversial Reviews**
   a. For relatively routine and noncontroversial applications (e.g., the approval of a new corn variety that contains the same transgene as a previously approved corn variety), the Coordinating Committee would determine, based on the application or pre-application summary, each of the regulatory agencies and issues likely to be involved in the review of the application. These determinations would be based on statutory and regulatory authority and/or a set of predetermined interagency agreements.

   b. The Coordinating Committee would prepare a draft response to the applicant and provide the predetermined agencies with a relatively brief (no more than 30-day) opportunity to request interagency consultation prior to sending the response letter to the applicant.

   c. In the absence of objections from the agencies, the Coordinating Committee would, within a predetermined period of time (weeks or months) after the receipt of the applicant's summary, provide the applicant with a letter setting out the relevant scientific and regulatory issues and the appropriate regulatory pathway for handling the application.

It is anticipated that all of the elements of this coordination proposal would be carefully spelled out in an interagency memorandum of understanding and made available to the public in user-friendly guidance published in the *Federal Register* and posted on the internet. The agencies could jointly seek public comments on the key elements of the reform, prior to its implementation. Whenever possible, agencies would utilize the same core data elements and studies to support their determinations, in order to prevent unnecessary redundancy.

COORDINATING COMMITTEE

While the EPA and FDA each have critical roles to play in their respective areas of expertise, only APHIS's scope of responsibility under the PPA, if new regulations are promulgated,[5] appears sufficiently broad to cover all transgenic plants and all potential impacts related to field testing and commercialization. Moreover, because its jurisdiction is trig-

5 APHIS is currently operating under regulations derived from the Federal Plant Pest Act that were promulgated in 1987 and rely on a "plant pest" determination (7 CFR Part 340). Regulations under the Plant Protection Act, which have not been drafted to date, would provide the agency with a broader reach of authority. See Chapter 2 for a more complete discussion.

gered by the earliest activity associated with regulated plants, in virtually every case APHIS is the agency that developers visit first. For these reasons, it may be appropriate for APHIS to be designated as the host for the Coordinating Committee for GE plants.

For products that fall within the jurisdiction of the EPA, the FDA, or both, the findings and decisions made by those agencies would be reflected in their own regulatory actions and in the permits and other actions taken by APHIS under the PPA and NEPA. Similarly, notifications for field trials submitted to APHIS would be reviewed simultaneously by the EPA, the FDA, or both, as appropriate. This structure does not anticipate that APHIS would be required to enforce the laws or regulations of the EPA, the FDA, or any other agency that may have jurisdiction over GE plants.[6] The interagency memorandum of understanding and implementing agency directives could instruct product developers to provide notice of intended uses, so that reviews by the EPA and FDA are triggered at appropriate times.

While APHIS would have significant new coordination and tracking responsibilities under this scheme, its regulatory responsibilities would not change. Under no circumstances would APHIS be authorized to overrule another agency's decision or usurp an agency's statutorily delegated authority. Any disputes that might arise between or among agencies would be resolved under the interagency memorandum of understanding, with provision for appeal to the OSTP, the CEQ, or the Domestic Policy Council, as is the current practice.

LEAD AGENCIES

In order to minimize redundancy, improve predictability, and best utilize personnel resources and traditional areas of expertise, the following product-based Lead Agencies could be designated:

- All food and feed products to the FDA
- All human and animal drugs and human biologics (including plant-made pharmaceuticals (PMPs)) to the FDA
- All animal biologics to the USDA
- All PIPs to the EPA
- All plant-made industrial products (PMIPs) to the EPA
- All nonspecified plants and plant products to APHIS

So, the EPA would be the Lead Agency for all PIPs. For those PIPs intended for food or feed use, the EPA would coordinate the reviews it conducts under FIFRA and the FDCA with the reviews conducted by the FDA. Even here, however, the FDA could be given lead responsibility to assess the allergenic potential of all GE foods, including PIPs. The FDA's assessments could be provided to the EPA for use in making its regulatory determinations for PIPs. The EPA would also serve as Lead Agency for all PMIPs. These reviews would be carried out

6 Therefore, to the extent that questions exist about the scope or enforceability of an agency's declared, or theoretical, authority over a GE plant or GE plant product, those issues are not rectified by this approach. This approach only serves to ensure better coordination among agencies so that products do not "slip through the cracks" and to eliminate redundancies in the current framework.

under the Toxic Substances Control Act (TSCA; 15 USC § 2601 et seq.) for any new chemical substances expressed in plants (as is currently the case for those made by microbes). In addition, the EPA could issue one or more TSCA significant new use rules in order to cover the potential environmental risks that could occur as a result of using plants to manufacture "existing" chemicals (i.e., those already on the market). APHIS would retain lead responsibility to assess the potential plant pest and noxious weed characteristics of all plants with pesticidal traits and all plants that express industrial chemicals or pharmaceuticals.

The FDA would be the Lead Agency for all products intended for use as food or feed (including food additives) with the exception of PIPs. But the FDA could have lead responsibility to assess the allergenic potential of PIPs as well as other proteins whose expression in food is modified via biotechnology. As an administrative reform, the FDA could strengthen its capacity to assess the allergenic potential of novel proteins in food. Ideally, the FDA would also be the Lead Agency for all PMPs except animal biologics, which are subject to USDA review. Pharmaceutical products subject to FDA review would include human and animal drugs, medical devices, and human biologics. APHIS would retain lead responsibility for assessing the potential plant pest and noxious weed characteristics of all plants that produce pharmaceutical substances; however, whether the FDA or APHIS has any current authority to assess, and regulate on the basis of, the potential of a pharmaceutical-producing plant to contaminate the food supply remains unclear.

The USDA would be the Lead Agency for animal biologics and all plants and plant products for which no other agency has the lead (e.g., trees, grasses, ornamentals, and flowers that do not express an otherwise regulated substance). APHIS would retain lead responsibility to assess the potential plant pest and noxious weed characteristics of all GE plants regardless of the Lead Agency assignments. As an administrative reform, APHIS could restructure its regulatory process in the context of implementing the PPA.

Appendix A: Acknowledgments

We at the Pew Initiative on Food and Biotechnology (PIFB) would like to thank the individuals listed below for contributing to our understanding of the regulatory issues surrounding agricultural biotechnology. These individuals include members of the Stakeholder Forum on Agricultural Biotechnology: Nearly 100 outside legal, scientific, and policy experts provided assistance to the Forum's efforts through briefings, presentations, research, analysis, and informal discussions; and those who took part in a joint meeting with the National Research Council. We would also like to give special notice to Jennifer Thomas-Larmer, whose wordsmithing abilities and understanding of regulatory issues made her the ideal editor of this report.

Stakeholder Forum Members

The Stakeholder Forum was a two-year dialogue process, convened in early 2001 by the PIFB, in which a diverse group of participants discussed and debated issues relating to agricultural biotechnology. Forum members were not involved in drafting this present report, and its contents do not reflect the views of the Forum nor any of its members. However, we at the PIFB are indebted to them for informing our own thinking on the topic of agricultural biotechnology over the course of the two-year process. The 18 Stakeholder Forum members who signed off on the Forum's final process report are listed below. (Their report can be read online at http://pewagbiotech.org/consensus/FinalReport.pdf)

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The following individuals contributed to the Stakeholder Forum process at various points during the dialogue. These individuals' knowledge and ideas, and in some cases the research and written analyses they produced for the Forum process, informed our thinking on the topic of agricultural biotechnology.

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As part of the Stakeholder Forum process, the PIFB sponsored a planning meeting in conjunction with the National Research Council's Committee on Agricultural Biotechnology, Health, and the Environment (CABHE). Titled "Exploring Genetic Modification of Plants: New Approaches and Implications for Definitions," the meeting was held on August 15, 2002. The following individuals took part.

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Appendix B: Data Requirements

As a rule, federal agencies require biotechnology developers to provide extensive information about genetically engineered (GE) plants and animals that are to be reviewed. This appendix provides examples of the kinds of data that developers are required to submit with various kinds of notifications and applications.

APHIS

Under its regulations at 7 CFR Part 340, the Animal and Plant Health Inspection Service (APHIS) requires the following data to accompany notification letters, permit applications, and deregulation petitions regarding GE plants.

The following information must accompany each **notification** letter:

- The scientific, common, or trade names, and phenotype
- The designation for the genetic loci, the encoded proteins or functions, and donor organisms
- The method of transformation
- The size of the introduction and origination and the destination (if movement) or field site location (if release)
- The 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

If a **permit for environmental release** is sought, the applicant must submit an application with the following information:

- All scientific, common, and trade names for the donor organism(s)
- The recipient organism(s)
- The vector or vector agent(s)
- A description of the molecular biology of the system (donor-recipient-vector) involved in the production of the regulated article
- A description of the activity of the anticipated or actual expression of the altered genetic material in the regulated article and a comparison to an unmodified organism (e.g., morphological or structural characteristics, physiological activities and processes, number of copies of inserted genetic material and the physical state of this material inside the recipient organism (integrated or extrachromosomal), products and secretions, growth characteristics)
- A detailed description of the purpose of the introduction, including a description of the proposed experimental and/or production design

- A detailed description of the processes, procedures, and safeguards that have been used or will be used to prevent contamination, release, and dissemination in the production of the donor organism, vector or vector agent, constituent of each regulated article that is a product, and the regulated article
- A detailed description of intermediate and final destinations, uses, and/or distribution of the regulated article (e.g., the location of greenhouses, laboratory or growth chambers, field trials, pilot projects, production, propagation, manufacture, proposed sale, and distribution), as well as a detailed description of the proposed processes, procedures, and safeguards to prevent escape and dissemination of the regulated article
- A detailed description of any biological material accompanying the regulated article during movement
- A detailed description of the proposed method of final disposition of the regulated article

An application for an **import or interstate movement permit** requires all of the above information except:

- a description of the activity of the anticipated or actual expression of the altered genetic material in the regulated article and a comparison to an unmodified organism;
- the purpose of the introduction; and
- safeguards against contamination, release, and dissemination in production.

To have a genetically engineered plant **deregulated,** the petitioner must explain the factual grounds for nonregulation, including the following:

- A description of the biology of the nonmodified recipient plant and information necessary to identify the recipient plant in the narrowest taxonomic grouping applicable
- Relevant experimental data and publications
- A detailed description of the differences in genotype between the regulated article and the nonmodified recipient organism, including all scientific, common, or trade names and all designations necessary to identify the donor organism(s), the nature of the transformation system (vector or vector agent(s)), the inserted genetic material and its product(s), and the required article
- A detailed description of the phenotype of the regulated article, including a description of known and potential differences from the unmodified recipient organism that would substantiate that the regulated article is unlikely to pose a greater plant pest risk than the unmodified organism from which it was derived, including but not limited to plant pest characteristics, disease and pest susceptibilities, expression of the gene product, new enzymes, or changes to plant metabolism, weediness of the regulated article, impact on the weediness of any other plant with which it can interbreed, agricultural or cultivation practices, effects of the regulated article on nontarget organisms, indirect plant pest effects on other agricultural products, transfer of genetic information to organisms with which it cannot interbreed, and any known information indicating that the regulated article poses a greater plant pest risk than the unmodified recipient organism
- Field test reports for all trials

The EPA

The data requirements of the Environmental Protection Agency (EPA) for the registration of a plant-incorporated protectant (PIP) are as follows (See EPA 2001a):

- Identification of the donor organisms and the nucleotide sequences that are inserted into the recipient plant
- Identification and description of the vector or delivery system used to move the nucleotide sequences into the recipient plant
- Identification of the recipient organism, including information on the insertion of the nucleotide sequences (e.g., stability of insertion)
- Chemical characterization of the plant-pesticide products
- Data and information on the levels of the pesticidal substances in the recipient plant, including any tissue specificity of expression
- An analysis of all potential nontarget species (including threatened or endangered species) that may be susceptible to the pesticidal substance
- Information on the presence of the pesticidal substance in edible portions of the crop
- Toxicology of the pesticidal substance
- Digestive fate of the pesticidal substance
- Potential allergenicity of the pesticidal substance
- Environmental fate of the pesticide

Claims of **confidential business information** to the EPA must include the following information, per 40 CFR 174.9 and 40 CFR Part 2, subpart B:

- The portions of the information that are alleged to be entitled to confidential treatment
- The period of time for which confidential treatment is desired by the business (e.g., until a certain date, until the occurrence of a specified event, or permanently)
- The purpose for which the information was furnished to the EPA and the approximate date of submission, if known
- Whether a business confidentiality claim accompanied the information when it was received by the EPA
- Measures taken by the business to guard against undesired disclosure of the information to others
- The extent to which the information has been disclosed to others, and the precautions taken in connection therewith
- Pertinent confidentiality determinations, if any, by the EPA or other federal agencies, and a copy of any such determination, or reference to it, if available

- Whether the business asserts that disclosure of the information would be likely to result in substantial harmful effects on the business's competitive position, and, if so, what those harmful effects would be, why they should be viewed as substantial, and an explanation of the causal relationship between disclosure and such harmful effects
- Whether the business asserts that the information is voluntarily submitted information, and, if so, whether and why disclosure of the information would tend to lessen the availability to the EPA of similar information in the future

The EPA also requires extensive test data for new chemicals being reviewed under the Toxic Substances Control Act (TSCA), as follows.[1]

Physical and Chemical Properties and Environmental Fate Data

Chromatograms
Spectra (ultraviolet, visible, infrared)
Density/relative density
Solubility in water
Melting temperature
Boiling/sublimation temperature
Softening point
Vapor pressure
Dissociation constant
Particle size distribution
Octanol/water partition coefficient
Henry's law constant
Volatilization from soil pH
Flammability
Explodability
Adsorption/desorption characteristics
Photochemical degradation
Viscosity
Odor
Hydrolysis
Thermal analysis
Chemical analysis
Chemical oxidation
Chemical reduction
Biodegradation
Transformation to persistent or toxic products

Health Effects Data

Mutagenicity
Carcinogenicity
Teratogenicity

1 See the EPA's web site (http://www.epa.gov/OPPTS_Harmonized/) for complete information regarding test data requirements for TSCA and the Federal Insecticide, Fungicide, and Rodenticide Act.

Neurotoxicity/behavioral effects
Pharmacological effects
Mammalian absorption
Distribution
Metabolism and excretion
Cumulative, additive, and synergistic effects
Acute, subchronic, and chronic effects
Structure/activity relationships
Epidemiology
Reproductive effects
Clinical studies
Dermatoxicity
Phototoxicity
Irritation
Sensitization
Allergy
Skin staining

Environmental Effects Data

Microbial bioassay
Algal bioassay
Aquatic macrophyte bioassay
Seed germination and root elongation
Seedling growth
Plant uptake
Acute toxicity to invertebrates
Life cycle test on invertebrates
Acute toxicity to fish
Early life stage (fish)
Avian dietary/reproduction
Bioaccumulation/bioconcentration
Model ecosystem studies
Physical environment impairment effects
Flesh staining of aquatic organisms

The FDA

The Food and Drug Administration (FDA) has issued guidance indicating the type of information that companies should provide to the agency during the voluntary consultation process. Developers are requested to submit to the FDA summaries of safety and nutritional assessments, which should "contain sufficient information for agency scientists to understand the approach the firm has followed in identifying and addressing relevant issues."

The FDA lists the following as the types of information that such summaries would ordinarily include (FDA 1997a):

- The name of the bioengineered food and the crop from which it is derived
- A description of the various applications or uses of the bioengineered food, including animal feed uses
- Information concerning the sources, identities, and functions of introduced genetic material
- Information on the purpose or intended technical effect of the modification, and its expected effect on the composition or characteristic properties of the food or feed
- Information concerning the identity and function of expression products encoded by the introduced genetic material, including an estimate of the concentration of any expression product in the bioengineered crop or food derived thereof
- Information regarding any known or suspected allergenicity and toxicity of expression products and the basis for concluding that foods containing the expression products can be safely consumed
- Information comparing the composition or characteristics of the bioengineered food to that of food derived from the parental variety or other commonly consumed varieties, with special emphasis on important nutrients and toxicants that occur naturally in the food
- A discussion of the available information that addresses whether the potential for the bioengineered food to induce an allergic response has been altered by the genetic modification
- Any other information relevant to the safety and nutritional assessment of the bioengineered food

In its proposal to require a pre-market biotechnology notification (PBN), the FDA indicated the need to remain flexible in its data requirements given the rapidly changing nature of agricultural biotechnology. The agency expressed the view that "the use of nontraditional strategies in the evaluation of food safety likely will become the norm as the use of rDNA technology expands...." The FDA also provided a seven-part format and general guidance for the proposed PBN, including information requirements, as follows (FDA 2001a):

1) A letter written by the developer attesting to the notifier's opinion that the bioengineered food is as safe as comparable food, the basis for selecting the comparable food, and that the intended use is in compliance with the applicable portions of the Food, Drug, and Cosmetic Act, either via "generally recognized as safe' (GRAS) or food additive status. In addition, the letter should attest that, to the best of the notifier's knowledge, the submission is a balanced review of information available on the bioengineered food, including information that is favorable or unfavorable to the safety, nutritional, or other regulatory issues associated with the food.

2) A synopsis including the same information recommended for inclusion in the pre-submission consultation.

3) A description of the status of any prior or ongoing evaluation(s) of the bioengineered plant or food derived from such a plant, including at other U.S. regulatory agencies (i.e., the EPA, APHIS), including issues still pending at those agencies, to ensure the appropriate and timely exchange of information between agencies about bioengineered pest-protected plants (PIPs). The notifier must also inform the FDA if the bioengineered food is or has been the subject of review by any foreign government, including the status of that review.

4) A description of the method of development of the bioengineered plant or food product, including:

   a) Characterization of the plant, including the scientific name, taxonomic classification, mode of reproduction, and pertinent history of development

   b) Construction of the vector used in the transformation of the parent plant, including:

      i) A thorough characterization of the genetic material (structural gene, open reading frames, regulatory sequences) intended for introduction into the recipient plant, and

      ii) the transformation methodology

   c) Characterization of the introduced genetic material, including:

      i) the number of insertion sites

      ii) number of gene copies inserted at each site

      iii) information on DNA organization within the inserts

      iv) information on potential reading frames that could express unintended proteins in the transformed plant

      v) data or information related to the inheritance and genetic stability of the introduced genetic material

      vi) discussion of other relevant data or information about the method of development not explicitly addressed in the PBN

5) A discussion of whether antibiotic resistance genes have been introduced into the bioengineered food, in accordance with the draft guidance issued in 1998 (FDA 1998). This guidance recommends that an evaluation of the safety of use of an antibiotic resistance marker, if it is expressed, should include an assessment of the safety of the protein or enzyme encoded by the gene, if present in food. The safety evaluation of the protein gene product encoded by an antibiotic resistance marker gene should include an assessment of potential systemic toxicity or allergenicity of the protein. Even if it is not expressed, developers should evaluate the potential for compromised efficacy of therapy (for humans or food animals) via horizontal transfer of the gene from plants to microorganisms in the gut of humans or animals, or from plant material to microorganisms in the environment.

6) A discussion of substances introduced into or modified in the food. A modified substance would include a substance that is present in the bioengineered food at an increased level relative to comparable food. Data and information that are required in this portion of a submission include:

   a) The identity of the introduced material, including gene and gene products

   b) The function of the introduced material

   c) The dietary exposure of the introduced material, or a statement as to why an estimate of dietary exposure is not needed to support safety

   d) An evaluation of the potential allergenicity of any introduced proteins, based on guidance developed as the result of experts at a conference on food allergy and bioengineered foods (April 18-19, 1994). This guidance has not yet been issued, although the Food and Agriculture Organization and the World Food Organization issued a report in 2001 on evaluating the allergenicity of genetically engineered foods that could serve as interim guidance (FAO and WFO 2001).

   e) Other information that may be relevant to safety not mentioned in the PBN

7) Data and information about the bioengineered food, including:

   a) Justification for the selection of particular food(s) as "comparable food" for purposes of establishing substantial equivalence. Comparable food would ordinarily be the parental variety or commonly consumed varieties of the parent plant.

   b) A discussion of historic uses of the comparable food

   c) If the intended technical effect is to alter the composition of the food, comparison of the composition and characteristics of another commonly consumed food with those characteristics (e.g., if the introduced trait is an oil not normally found in the parental variety, comparison to a plant in which that oil is normally found may be appropriate). The nature of the comparison should be resolved during the consultation process.

   d) A comparison of the composition and characteristics of the bioengineered food to the comparable food, with emphasis on:

      i) Significant nutrients

      ii) Naturally occurring toxicants and antinutrients

      iii) Intended changes to the composition of the food

      iv) Other information that may be relevant to the safety, nutritional, or other regulatory assessment of the bioengineered food

   e) A narrative explaining the basis for the notifier's view that the bioengineered food is as safe as the comparable food, and otherwise in compliance with the Food, Drug, and Cosmetic Act.

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Appendix D: Abbreviations

ADCA	Animal Damage Control Act
AHPA	Animal Health Protection Act
APHIS	Animal and Plant Health Inspection Service (USDA)
AQ	animal quarantine
AWA	Animal Welfare Act
Bt	*Bacillus thuringiensis*
CBER	Center for Biologics Evaluation and Research
CBI	confidential business information
CDER	Center for Drug Evaluation and Research
CEQ	Council on Environmental Quality (The White House)
CFR	Code of Federal Regulations
CFSAN	Center for Food Safety and Applied Nutrition (FDA)
CVM	Center for Veterinary Medicine (FDA)
DNA	deoxyribonucleic acid
DOI	Department of Interior
EA	environmental assessment
EIS	environmental impact statement
EPA	Environmental Protection Agency
EPIA	Egg Products Inspection Act
EUP	experimental use permit
FDA	Food and Drug Administration
FDCA	Food, Drug, and Cosmetic Act
FET	Foundation on Economic Trends
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FMIA	Federal Meat Inspection Act
FNWA	Federal Noxious Weed Act
FOIA	Freedom of Information Act
FONSI	finding of no significant impact
FPPA	Federal Plant Pest Act
FSIS	Food Safety and Inspection Service (USDA)
FWS	Fish and Wildlife Service (DOI)
GE	genetically engineered
GLP	good laboratory practice

GMP	good manufacturing practice
GRAS	generally recognized as safe
GRASE	generally recognized as safe and effective
IFA	Infant Formula Act
INAD	investigational new animal drug
MCAN	microbial commercial activity notice
NADA	new animal drug application
NEPA	National Environmental Policy Act
NMFS	National Marine Fisheries Service
NRC	National Research Council (National Academy of Sciences)
OSTP	Office of Science and Technology Policy (The White House)
PBN	pre-market biotechnology notification
PCAN	plant commercial activity notice
PIFB	Pew Initiative on Food and Biotechnology
PIP	plant-incorporated protectant
PMIP	plant-made industrial product
PMN	pre-manufacturing notice
PMP	plant-made pharmaceutical
PPA	Plant Protection Act
PPIA	Poultry Products Inspection Act
rBST	recombinant bovine somatotropin
rDNA	recombinant deoxyribonucleic acid
SNUR	significant new use rule
TERA	TSCA experimental release application
TSCA	Toxic Substances Control Act
USC	U.S. Code
USDA	U.S. Department of Agriculture
VCP	viral coat protein
VSTA	Virus Serum Toxin Act