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Report to the Chairman, Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

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FOOD SAFETY AND QUALITY

Innovative Strategies May Be Needed to Regulate New Food Technologies

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Resources, Community, and
Economic Development Division

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July 26, 1993

The Honorable John Dingell
Chairman, Subcommittee on Oversight
and Investigations
Committee on Energy and Commerce
House of Representatives

Dear Mr. Chairman:

In the past, the introduction of technologies—such as pasteurization, vitamin fortification, and refrigeration—vastly improved food quality and safety. Today, new food technologies—such as new biotechnology—hold similar promise. Yet hopes for achieving a healthier, more varied, and less expensive diet through new food technologies are offset by fears of their unpredictable effects on human health and the environment. As the federal agency responsible for ensuring food quality and safety, the Food and Drug Administration (FDA) oversees new food technologies to protect public health and encourage innovation.

In response to your request for information on this complex and controversial subject, we (1) identified and described selected new food technologies, (2) determined FDA's responses to these technologies and reviewed the processes that the agency uses to determine whether they are safe for consumers, and (3) identified unresolved regulatory issues associated with FDA's regulation of new food technologies.

Results in Brief

Although there is no generally accepted definition of "new food technologies," diverse new food processes and products are transforming the nation's food supply. Rapid advances in science and technology and attempts by industry to respond to changes in consumers' demographics and dietary preferences have encouraged the development of new foods and food ingredients as well as new methods of producing, processing, preserving, and packaging foods. Among the most important of these are (1) new biotechnology or genetic engineering, (2) novel macro ingredients—food additives intended to replace major dietary components such as fats, (3) functional foods—food substances designed to lower the risk or delay the onset of certain diseases, and (4) new types of packaging for foods.

FDA has responded to new food technologies in a variety of ways. First, FDA has applied the existing regulatory framework to the products of new food technologies, classifying new foods and food ingredients on the basis of their characteristics and intended use—not on their method of manufacture. This classification determines whether new food products are subject to FDA's oversight only after they have entered the market (postmarket surveillance) or whether they require FDA's approval before they may enter the market (premarket approval). Second, FDA has conducted and sponsored research to keep pace with technological developments. Third, FDA has created new positions, reorganized offices, and performed other activities to oversee the quality and safety of new food technologies.

FDA's responses to new food technologies have left several controversial scientific and regulatory issues unresolved. These issues have raised three broad policy questions. First, is the regulatory framework for food and food ingredients, established before the advent of today's technologies, adequate for ensuring the safety of new food technologies? Second, are FDA's enforcement authority and resources adequate to oversee the safety of new food technologies introduced into the marketplace? Third, how can the government strike a balance between regulating industry to protect consumers' health and giving industry the freedom to develop and market new food products and processes? A review of the existing regulatory framework could suggest innovative strategies for ensuring the safety and fostering the development of new food technologies, especially of those that promise to improve consumers' health.[1]

Background

Under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended (21 U.S.C. 301 et seq.), growers, manufacturers and retailers are primarily responsible for ensuring the safety of the foods and food ingredients that they market, including the products of new food technologies. Nonetheless, the nation's approximately 250 million consumers rely on FDA to oversee the industry and to ensure that over $240 billion worth of domestic foods and $15 billion worth of imported foods are safe, sanitary, nutritious, wholesome, and truthfully labeled. Except for meat and poultry products, for which the U.S. Department of Agriculture (USDA) is responsible, and egg products, for which FDA shares responsibility with USDA, FDA is responsible for ensuring that industry properly produces, processes, and distributes foods marketed in interstate commerce.

[1]See Food Safety and Quality: Uniform Risk-based Inspection System Needed to Ensure Safe Food Supply (GAO/RCED-92-152, June 26, 1992).

FFDCA sets out a framework for FDA's regulation of food and food ingredients (see app. I). This framework, which has evolved over time—partly in response to past introductions of new food technologies—reflects the complexity of the nation's food supply. Within this framework, the classification of a food or food ingredient determines whether it is subject only to FDA's postmarket surveillance or whether it requires FDA's premarket approval. FFDCA establishes categories for food and food ingredients and specifies legal standards of safety and regulatory requirements for each of these categories as follows:

- Foods are whole foods—such as fruits, vegetables, and grains—and processed foods made from whole foods. Food products may be marketed without FDA's premarket approval. To remove a food product from the market, FDA must prove that it is adulterated (e.g., contains an added substance that may render the food injurious to health) and/or that it is misbranded (e.g., its labeling is false or misleading).
- Food additives are substances that are intended to become components of food, directly or indirectly, or otherwise affect the characteristics of food. This category excludes substances regulated under other categories. A food additive may be any substance used in producing, processing, or packaging food, including a source of radiation used to treat food. Uses of food additives require FDA's premarket approval. FFDCA prohibits food additives that cause cancer in humans or animals.
- Color additives are dyes, pigments, or other substances capable of imparting color, excluding those substances that impart color but are intended for other purposes in food. Uses of color additives require FDA's premarket approval and are subject to the same kinds of regulatory requirements as food additives.
- Food substances that are prior sanctioned or generally recognized as safe (GRAS) are exempted from regulation as food additives and do not require FDA's premarket approval. Prior sanctioned substances were approved by either FDA or USDA before the Congress enacted the Food Additives Amendment in 1958. GRAS substances include both food ingredients with a history of common use in food before 1958—such as salt, pepper, and vinegar—and substances introduced after 1958 that scientists have generally agreed, on the basis of published scientific studies, are safe when used in food. Manufacturers and others may themselves determine that a substance is GRAS without obtaining FDA's approval or notifying the agency. However, GRAS substances are subject to FDA's postmarket surveillance, and FDA may challenge a manufacturer's GRAS determination and ultimately require the submission of a food additive petition or stop the marketing of products containing the substance.

- Animal feed, additives, and drugs include substances intended for animal use that can affect the safety of animal products eaten by consumers. These substances are generally subject to the same requirements under FFDCA as similar products intended for human use.

Generally, manufacturers are responsible for determining the appropriate regulatory category for a new food or food ingredient. In addition, they are responsible for determining whether a change in the composition, use, or method of manufacturing a product is sufficient to change its regulatory status. For example, the manufacturer must determine whether a new food ingredient falls within the scope of an existing food additive regulation, requires a new food additive regulation, or is exempt from regulation as a food additive because it is GRAS. Because these determinations may be complex, FDA encourages manufacturers to refer regulatory questions to the agency before marketing new products.

To conduct postmarket surveillance, FDA (1) inspects domestic food establishments (e.g., manufacturing and processing facilities) to ensure compliance with federal laws, regulations, and good manufacturing practices and (2) inspects imported food products at the port of entry to ensure compliance with the same safety and labeling requirements established for domestic foods. To conduct premarket reviews, FDA requires manufacturers to submit a petition with data to demonstrate the safety of a substance's intended use. FDA then reviews the petition and data and determines whether it can establish a regulation specifying the conditions for the safe use of the substance. In fiscal year 1992, FDA dedicated about 2,700 staff years and almost $200 million to food safety efforts, including oversight of new food technologies.

What Are New Food Technologies?

No single definition of "new food technology" is generally accepted among food scientists, government regulators, and industry and consumer representatives. In the broadest sense, however, the term may be applied to any food product or process that is "new" at the farm, factory, or retail store. New food technologies can include novel foods and food ingredients, new formulations or processes to produce an existing product, new packaging, and new uses of an existing product or process. New food technologies can range from slight changes in existing products to revolutionary changes in the composition, use, form, or consumption of products. Safety and nutritional concerns related to new food technologies are also diverse and include concerns about both the extent and rate of change in the American diet.

Although no single definition of new food technology prevails, informed observers generally agree that food technology is rapidly changing. The number of new food products introduced annually to the retail grocery market has increased from just over 2,000 in 1980 to over 12,000 in 1992. Most of these were slight changes to existing products. Nonetheless, FDA predicts that the number and variety of new food products will continue to grow as the industry's technological capacity expands. Moreover, food scientists and others believe that certain new food technologies, especially advances in new biotechnology, could transform the food supply and redefine the very idea of food.

We examined four types of new food technologies.

- New biotechnology, or genetic engineering, uses modern techniques—such as recombinant deoxyribonucleic acid (rDNA), or gene splicing—to modify genes to produce commercial products and perform industrial processes. For example, genetically altered bacteria have been used to produce an enzyme called chymosin, or rennin, that curdles milk to make cheese and other dairy products. This enzyme has traditionally been derived from the stomachs of calves.
- Novel macro ingredients are substances intentionally added to food in relatively large quantities to modify caloric intake or replace major dietary components, such as fats and sugars. These ingredients have the potential to provide attractive food choices that may be beneficial in reducing weight and managing diets. FDA is reviewing a food additive petition for Olestra, a sucrose polyester compound that is intended to replace fat in processed snack foods, such as potato chips, without supplying calories.
- Functional foods are food products to which naturally occurring chemicals—found in many fruits, vegetables, grains, herbs, and spices—have been added in an attempt to lower the risk of certain diseases, such as cancer. For example, beta carotene, the yellow-orange pigment found in carrots and other vegetables, may be concentrated and added to food products to try to inhibit lung cancer.
- New packaging technologies include new methods of packaging refrigerated foods as well as various types of microwaveable and recyclable packaging.

Appendixes II through V discuss these new food technologies in detail, including for each (1) a definition, (2) examples and applications, (3) food safety concerns, (4) FDA's response, and (5) unresolved regulatory issues. Regulatory issues that cut across specific technologies are discussed in appendix VI.

FDA's Responses to New Food Technologies Are Diverse

As diverse as the new food technologies themselves, FDA's responses include (1) regulating and monitoring the products of the new technologies, (2) conducting and sponsoring research, and (3) creating positions, reorganizing offices, and performing other activities.

FDA Applies the Existing Regulatory Approach

Neither FFDCA nor FDA regulations specifically provide for "new food technologies." In general, FDA applies the same regulatory framework for food and food ingredients to ensure the safety of products developed by new food technologies as it does to ensure the safety of products developed by existing technologies. Therefore, whether a new food technology is subject only to FDA's postmarket surveillance or whether it requires FDA's premarket approval depends on how the food produced by the new technology is classified and regulated under FFDCA.

According to FDA, FFDCA focuses on the product that is introduced into interstate commerce rather than on the method of manufacturing the product. Hence, FDA's safety and regulatory policies focus on the characteristics and intended use of the final commercial food or food ingredient introduced. Except for low-acid and acidified canned foods, infant formula, and certain food ingredients, FDA typically does not regulate how a food or food ingredient is produced as long as it is produced in a safe and sanitary manner. FDA may, however, review the manufacturing process during its premarket review of a food ingredient because, according to FDA officials, the process, whether old or new, can affect the safety and nutritional characteristics of the end product. Once FDA has approved a new food ingredient, manufacturers are generally free to use or modify any process to produce the ingredient without notifying FDA. The final ingredient must, however, comply with FDA's regulations and may not introduce contaminants that could render the food injurious to health or new substances that would themselves require premarket approval.

FDA has issued policy statements to clarify how it will use the existing regulatory framework for food and food ingredients to ensure the safety of new food technologies. For example, in May 1992, FDA published a policy statement on food derived from new plant varieties, including plants modified through new biotechnology.[2] Under this policy, FDA will regulate

[2]Although FDA's policy applies to food derived from new plant varieties that have been genetically modified by traditional as well as new techniques, this report focuses on the application of the policy to food products developed through new biotechnology (or genetic engineering, as used in this report.) (See app. II.)

the safety of genetically engineered whole foods primarily through the postmarket adulteration provisions of FFDCA. Thus, if FDA finds that a genetically engineered plant contains a higher-than-intended level of a naturally occurring toxin or contains an unexpectedly harmful substance that may render the food injurious to health, FDA can declare the food item adulterated and in violation of FFDCA. Like previously introduced whole foods derived from plants modified by traditional cross-breeding, genetically engineered whole foods generally do not require premarket review. Although FDA stated that it would not require genetically engineered food products to be labeled as such, the agency published a notice in the Federal Register in April 1993 requesting data and information on this issue in response to public comments on its 1992 policy statement.

Under FDA's policy, a substance that is intended or expected to become a component of food through genetic engineering (i.e., a transferred gene and/or the traits it may express, called expression products) may be subject to premarket review as a food additive unless the substance is GRAS or otherwise exempt from regulation as a food additive. Genetically engineered substances that do not differ substantially from historically safe or GRAS substances may be considered GRAS and exempt from FDA's premarket review. However, genetically engineered substances that differ substantially in structure, function, or composition from substances currently found in food or that otherwise raise a safety question (e.g., a novel sweetener) may not be considered GRAS and may require FDA's premarket approval as a food additive. FDA's biotechnology policy statement provides guidance to manufacturers to help them categorize their products.

FDA first approved a genetically engineered food product in 1990, when it classified the chymosin produced by genetically altered bacteria as GRAS. FDA is currently reviewing other genetically engineered products, including a growth hormone for dairy cows and a slow-ripening tomato (see app. II), as well as products of other new food technologies, such as the noncaloric sucrose polyester fat substitute (see app. III).

FDA Conducts and Sponsors Research

In addition to reviewing individual products developed by new food technologies, FDA conducts and sponsors research to identify emerging technologies and to assess the impact of certain technologies on nutritional quality and food safety. FDA believes that its scientists must

conduct research to keep pace with technological advances and develop expertise to evaluate the safety of new products and processes.

To promote research on new food technologies, FDA, among other things, helps to support the National Center for Food Safety and Technology in Chicago, Illinois—a research and education consortium of government, academia, and industry. The National Center was created in 1988 to study the effects of processing and packaging technologies, as well as of biotechnology, on food safety and quality. FDA also conducts research with the National Cancer Institute on the nutritional safety of foods containing extracts of naturally occurring food compounds believed to inhibit certain cancers.

FDA Has Made Organizational and Other Changes

FDA also has created new positions, changed its organizational structure, and performed other activities in response to new food technologies. For example, in 1986 it created a position within its Center for Food Safety and Applied Nutrition (CFSAN) to coordinate the regulation of genetically engineered foods and food ingredients, and in 1989 it created a multipurpose biotechnology laboratory in Dallas, Texas. In 1990, FDA created a special branch within CFSAN to identify and assess safety questions posed by novel food additives, such as novel macro ingredients, and to develop policies for regulating these additives. Recently, FDA conducted a management study of CFSAN's programs and activities, reorganized CFSAN, and established an advisory committee on food safety issues.

To communicate FDA's positions on safety and regulatory issues presented by new food technologies, agency officials have published articles in scientific and policy journals, provided technical guidelines for manufacturers, and issued policies, such as the policy on new biotechnology. They have also held meetings with consumer and environmental groups and with members of industry, sponsored or participated in conferences, and provided information on new food technologies to congressional committees and others.

Unresolved Issues Raise Broad Policy Questions

FDA's responses to new food technologies have left several controversial scientific and regulatory issues unresolved (see apps. II-VI). Collectively, these issues raise three broad policy questions:

- Is the existing regulatory framework for food and food ingredients adequate to ensure the safety of new food technologies?
- Does FDA have adequate enforcement authority and resources to oversee the safety of new food technologies introduced into the marketplace?
- How can the government strike a balance between regulating industry to protect consumers' health and giving industry the freedom to develop and market new food products and processes?

Adequacy of Regulatory Framework Is Questioned

Critics of FDA's regulation of new food technologies have questioned the adequacy of the existing regulatory framework to ensure the safety of these technologies. Specifically, consumer and environmental groups are concerned because premarket approval is not required either for new food products or for new food substances that manufacturers and others have determined are GRAS. These groups are also concerned because FDA has limited control over new uses of approved substances and new or modified manufacturing processes. In addition, some industry and FDA officials believe that certain new substances, such as functional foods, may not fit into the existing categories for food and food ingredients. Moreover, some FDA officials and others believe that the existing categories, which generally establish legal standards of safety that depend on the substance's intended use rather than on the risks that the substance may present to human health, may inhibit FDA's allocation of resources to review riskier substances. Consumer and environmental representatives, some industry officials, and others have suggested alternative approaches for regulating new food technologies, but these proposals have also provoked controversy.

Neither FFDCA nor its legislative history specifically addresses how FDA should treat food derived from new plant varieties, according to FDA officials. Because FDA intends to regulate genetically engineered plants as foods and generally not subject them to premarket review or label them as products of new biotechnology, consumer and environmental groups are concerned that consumers may be exposed to hazards, such as new toxins or allergens. These groups believe that FDA should (1) regulate genetically engineered foods under the food additive provisions of FFDCA and require premarket safety testing; (2) require manufacturers to notify the agency before marketing any genetically engineered food substance, including those that manufacturers themselves have determined are GRAS; and (3) require labeling of all genetically engineered foods.

At issue in the debate over regulating genetic engineering is whether the new biotechnology differs so fundamentally from traditional biotechnology, or cross-breeding, that FDA should regulate the process as well as the results of the process. Consumer and environmental groups believe that new biotechnology poses new and unique safety concerns because it allows genetic modifications, such as the insertion of a gene from one species into another, that could not be achieved through traditional cross-breeding. Such modifications, these groups argue, could create unforeseen hazards for consumers—the possibility, for example, that a protein could be added to tomatoes that could inadvertently cause an allergic reaction in a consumer who had not previously been allergic to tomatoes. According to these groups, more is required to protect consumers from the potential hazards of new biotechnology than FDA's postmarket surveillance of industry's determinations of safety. In their view, premarket review is necessary.

In contrast, scientists from government, industry, and academia see the new biotechnology as an extension of the old—as a more rapid and precise method of modifying genes. They do not believe that the products of new biotechnology present any different or greater safety concerns than foods developed by traditional plant breeding. According to FDA officials, the agency bases its policy on its scientific judgment that many of the substances expected to become components of food through the use of genetically modified plants that are approaching commercialization are not significantly different from substances already in traditional food. Therefore, they believe that requiring premarket review for all genetically engineered food substances would impose an undue burden on industry and discourage innovation without significantly enhancing consumers' safety. In addition, FDA officials note that increasing the requirements for premarket review without increasing the agency's resources would slow the review process.

The development of genetically engineered foods and novel macro ingredients has also raised questions about whether manufacturers and others should retain their authority to determine that a new substance is GRAS and therefore exempt from FDA's premarket review and approval. For example, because new food products may incorporate GRAS substances—such as oat fiber, beta carotene, or egg white—in previously untested quantities, concentrations, or forms, some consumer advocates and others, including some FDA officials, have questioned whether the laws leaving GRAS determinations up to industry adequately protect public health. Industry officials and others have argued, however, that

manufacturers are responsible for ensuring the safety of their food products. In their view, it would be unreasonable to spend government resources to evaluate a product that did not pose a significant risk to consumers.

Although manufacturers are responsible for ensuring the safety of new uses of previously approved substances and new or modified manufacturing processes, such changes have posed safety concerns. For example, the high temperatures created in microwave ovens can cause chemicals in approved packaging materials to move from the materials to the food. Because the food additive regulations for the use of these materials do not limit the temperatures to which the materials can be exposed, the public may be exposed to low levels of chemical contaminants in their food. FDA is reviewing the results of manufacturers' research to determine whether and how to revise the regulations for the use of these materials. A change in a foreign producer's manufacturing process may have been a factor in an incident involving the dietary supplement L-tryptophan. Although the exact cause of the problem has not yet been identified, exposure to certain L-tryptophan products was linked to about 1,500 illnesses and 38 deaths in the late 1980s (see app. II).

New food technologies, such as functional foods, that incorporate specific food components to lower the risk of disease may not fit the existing categories for food and food ingredients. FDA officials and others believe that these products may blur, if not erase, the legal boundary line between foods and drugs. Depending on the intended use and form of a product, FDA may classify it as a food, drug, or both. This classification is important because drugs have to meet more stringent efficacy requirements than food additives, and their manufacturers have to comply with stricter controls over manufacturing, marketing, and record-keeping. However, drugs are evaluated on the basis of both risks and benefits, whereas food additives are evaluated on the basis of risks alone. Some advocates of functional foods believe that neither classification provides manufacturers with sufficient incentive to develop these new products and that a new system is needed for regulating these products.

Some FDA officials and others have criticized the existing regulatory framework because it does not categorize food and food ingredients on the basis of risk to consumers' health and may therefore require FDA to spend resources reviewing substances that pose little or no risk to consumers. For example, the food additive provisions of FFDCA require premarket approval of packaging materials that migrate to food regardless

of the effect of this migration on the food's safety. FDA plans to establish a regulation that would specify a level below which it would not consider the substances as food additives and therefore as subject to premarket approval. In 1979, the National Academy of Sciences recommended that the Congress replace the existing categories with a single standard based on risk to consumers' health.

Although FDA believes that the existing framework for food and food ingredients is adequate for regulating the products of new food technologies, others have proposed alternative approaches that range from relatively minor to full-scale revisions of the framework. For example, several observers have proposed that FDA establish a premarket notification system to bridge the existing gap between the absence of premarket review and approval for some new food products and processes and the extensive premarket review required for new food additives. Although specific proposals differ, such a system would generally require manufacturers to notify FDA before they marketed the product of a new food technology, such as a genetically engineered tomato. Proponents believe that such a system would better enable FDA to evaluate and monitor the safety of new food technologies and products and could promote consumers' acceptance of new technologies—without which the benefits of the new technologies could be lost. However, critics of the proposals, including some FDA officials, think that the agency lacks explicit authority to establish such a system, that the establishment of such a system would shift the burden of demonstrating a product's safety from the manufacturer to FDA, and that the costs of administering such a system would outweigh the benefits to consumers' health. The Office of Technology Assessment has recommended that the Congress hold hearings to explore regulatory options, including the establishment of a premarket notification system.[3]

Limitations in Enforcement Authority and Resources May Hinder FDA's Oversight

To oversee the safety of new food technologies, FDA relies extensively on postmarket surveillance of domestic establishments and imported products. However, as we have previously reported, limitations in enforcement authority affect FDA's ability to conduct postmarket surveillance.[4] For example, food producers and manufacturers are generally not required to register with FDA or to inform the agency that

[3]Office of Technology Assessment, A New Technological Era for American Agriculture, OTA-F-474 (Washington, D.C.: Aug. 1992).

[4]See Food Safety and Quality: Uniform, Risk-based Inspection System Needed to Ensure Safe Food Supply (GAO/RCED-92-152, June 26, 1992) and other GAO reports listed in footnotes and in app. VI.

they are in business. Hence, FDA is not aware of, and therefore does not oversee and inspect, some domestic food establishments. In addition, restrictions on FDA's access to manufacturers' production and distribution records impair the agency's surveillance of products suspected of being adulterated. Legislative proposals to expand FDA's enforcement authority have met with objections from industry and others.

According to current and former FDA officials, industry and consumer representatives, and academics, FDA does not have adequate resources to meet its current work load and will experience further strains as the products of new food technologies are introduced. Many have cited deficiencies in FDA's facilities and equipment, as well as in the number of staff and the range of scientific expertise represented within the agency. For example, according to FDA officials, the agency has had difficulty attracting new packaging specialists because its salaries are not competitive with private industry's. As a result, these officials believe that FDA does not have the in-house ability to perform needed research on new methods of packaging. FDA has been trying to acquire wider expertise through research at the National Center and other means. Moreover, because of resource constraints and competing priorities for inspection, such as blood banks, FDA officials inspected only one-third as many domestic food establishments in fiscal year 1992 as they did in fiscal year 1981. The Congress recently authorized FDA to charge user fees for approving new prescription drugs and to use these fees to accelerate the approval process. However, these fees are not available for funding the agency's food programs. Previous proposals to establish user fees for FDA's food programs have led to disagreements about whether the fees should supplement or replace current funding.

Until recently, FDA has been limited in its ability to manage its resources for food programs effectively because it has lacked a strategic plan. Many people whom we interviewed, both inside and outside the agency, thought that FDA was not as well prepared as it needed to be to regulate new food technologies. Although the agency has responded to specific food safety problems and issues associated with new food technologies, it has not—since 1984, when it completed its last strategic plan—had a mechanism to integrate and establish long-term priorities for its efforts. FDA is now developing strategic plans for the agency as a whole and for its food programs in particular.

Striking Proper Regulatory Balance Is Critical

Striking the proper balance between regulating industry and giving industry the freedom to develop and market new food products and

processes is critical for ensuring the safety and promoting consumers' acceptance of, and fostering industry's investment in, new food technologies. Consumers rely on industry and FDA to ensure that new food products and processes introduced into the marketplace are safe. However, as interested parties have observed, if consumers do not have confidence in such assurances, they will not accept the products of new food technologies, and the benefits of the new products may be lost. Industry representatives acknowledge that they need FDA's backing to allay consumers' concerns about the new food technologies. Nonetheless, they do not believe that the risks posed by these technologies are significant enough to warrant extensive and costly premarket oversight. In addition, they are concerned that uncertainty over the classification and regulation of new food products could create barriers to investment and innovation in new food technologies.

According to scientists from FDA, industry, and academia, the key to striking the proper regulatory balance is to review new food technologies on the basis of the best scientific assessment of the risks to consumers' health. However, consumer and environmental groups are concerned that, in some cases, insufficient data and experience are available to assess these risks. In addition, some believe that criteria other than health risks should be considered, such as socioeconomic factors. For example, some consumer advocates believe that genetically engineered food should be labeled as such because consumers have a right to know what they buy and eat. Still others believe that FDA should be allowed to weigh both the benefits and the risks of certain food substances.

There is no simple answer to these complex and controversial questions. Conflicting interests and values have made it difficult in the past to revise FFDCA's basic food safety provisions. Last June, we recognized similar obstacles to revamping the federal food safety inspection system in our report Food Safety and Quality: Uniform, Risk-based Inspection System Needed to Ensure Safe Food Supply (GAO/RCED-92-152, June 26, 1992). We recommended that the Congress consider, among other things, creating a blue ribbon panel to develop a regulatory model for federal food safety oversight. We concluded that such a panel might be the most realistic way to develop broad-based agreement on the organizational and legislative changes needed to modernize the food safety system. In developing a new model for federal food safety oversight, the panel could also review the adequacy of the regulatory framework for food and food ingredients. In addition, the panel could explore options for regulating new food technologies, such as creating an expedited premarket notification system

to strike a balance between no premarket review of new foods and extensive premarket review of food additives. Even if the panel decided that no changes were necessary to the existing law, regulations, or operations, the review process itself might help to assure consumers that the government was prepared to deal with new food technologies.

Conclusion

Because the existing legislative guidance predates today's new food technologies and FDA's application of this guidance has been controversial, it may now be time to review the regulatory framework for food and food ingredients. A formal review of this framework could identify innovative strategies for striking the optimum regulatory balance between protecting consumers' health and fostering development. A review could also evaluate the adequacy of FDA's enforcement authority and resources to meet the responsibilities set forth in laws and regulations.

Matter for Congressional Consideration

We have recommended that the Congress create a blue ribbon panel to develop a model for inspection and food safety enforcement on the basis of the public health risks posed by food products and processes. As part of the panel's mandate, the Congress may wish to direct the panel to review the regulatory framework for food and food ingredients and to explore innovative strategies for regulating new food technologies, such as the creation of an expedited premarket notification system.

Agency Comments

We discussed the information in this report with officials in FDA's Center for Food Safety and Applied Nutrition (including the Deputy Director for Programs), Center for Veterinary Medicine, Office of General Counsel, Office of the Commissioner, and Office of Regulatory Affairs, and we have included their comments where appropriate. FDA officials generally agreed with the accuracy and completeness of the facts presented. However, as requested, we did not obtain written agency comments on a draft of this report.

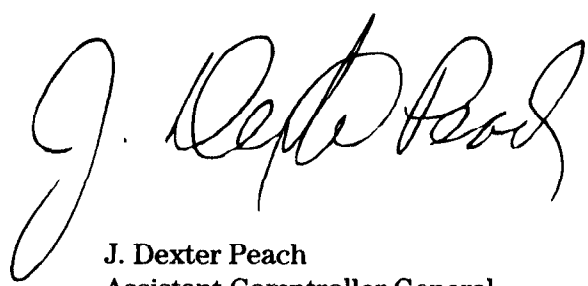
We conducted our work in accordance with generally accepted government auditing standards. Appendix VII contains a detailed discussion of our objectives, scope, and methodology.

As arranged with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from the

date of this letter. At that time, we will send copies to interested congressional committees, the Secretary of Health and Human Services, and the Commissioner of FDA. We will make copies available to others upon request.

This work was performed under the direction of John W. Harman, Director, Food and Agriculture Issues, who may be reached at (202) 512-5138 if you or your staff have any questions. Major contributors to this report are listed in appendix VIII.

Sincerely yours,



J. Dexter Peach
Assistant Comptroller General

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Abbreviations

BST	bovine somatotropin
CFSAN	Center for Food Safety and Applied Nutrition
CVM	Center for Veterinary Medicine
EMS	eosinophilia-myalgia
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
GRAS	generally recognized as safe
HACCP	hazard analysis critical control points
HHS	Department of Health and Human Services
NLEA	Nutrition Labeling and Education Act
OTA	Office of Technology Assessment
PCB	polychlorinated biphenyl
ppb	parts per billion
rBGH	recombinant bovine growth hormone
rDNA	recombinant deoxyribonucleic acid
USDA	U.S. Department of Agriculture

Major Food Safety Provisions of the Federal Food, Drug, and Cosmetic Act

Under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended (21 U.S.C. 301 et seq.), the Food and Drug Administration (FDA) is the federal agency responsible for overseeing the safety of food marketed in interstate commerce except for meat and poultry, which are regulated by the U.S. Department of Agriculture (USDA), and egg products, which are regulated by both FDA and USDA. FFDCA sets out a framework for regulating food and food ingredients.[1] This framework, which has evolved over time—partly in response to past introductions of new food technologies—reflects the complexity of the nation's food supply. Under this framework, a food or food ingredient is classified, and its classification determines whether it (1) is subject to FDA's oversight only after it has entered the market (postmarket surveillance) or (2) is required to obtain FDA's approval before it enters the market (premarket approval). This appendix describes the major categories for food and related substances under FFDCA, including

- food,
- food and color additives,
- prior sanctioned and generally recognized as safe (GRAS) substances, and
- animal feeds, additives, and drugs.

This appendix also describes the applicable legal standard of safety and identifies when premarket approval may be required. (See table I.1.)

Generally, the food safety provisions of FFDCA categorize food and related substances on the basis of their use or way of entering the nation's food supply rather than on the basis of their risks or benefits to human health. Some substances fall into more than one category, depending on their use.

[1]Other laws affecting FDA's food safety activities include the Public Health Service Act, Pesticide Monitoring Improvements Act of 1988, Egg Products Inspection Act, Safe Drinking Water Act, Federal Anti-Tampering Act, and Federal Import Milk Act.

Table I.1: General Overview of Selected Food Safety Provisions of the Federal Food, Drug, and Cosmetic Act

Substance category	Description	Legal standard of safety	Premarket approval required?
Food	Article used for food or drink for people or animals, chewing gum, and article used as a component of any such article.	Adulterated if, among other things, food contains any added substance that may render it injurious to health; contains any naturally occurring substance that ordinarily renders it injurious to health; or is filthy, is produced under insanitary conditions, or contains an unapproved ingredient.	No (unless the food is also a food additive)
Food additive	Any substance whose intended use results or may reasonably be expected to result, directly or indirectly, in its becoming a component of food or otherwise affecting the characteristics of any food. Excludes prior sanctioned ingredients, GRAS substances, color additives, new animal drugs, and certain pesticide residues.	"Safe" (i.e., reasonable certainty of no harm); Delaney Clause applies.	Yes
Color additive	Dye, pigment or other substance capable of imparting color, excluding a substance that imparts color but is intended for another purpose in food.	"Safe" (i.e., reasonable certainty of no harm); Delaney Clause applies.	Yes
Prior sanctioned substance	Substance whose use was sanctioned or approved by FDA or USDA before 1958.	Food containing the substance is adulterated if the substance may render the food injurious to health.	No
GRAS substance	Substance generally recognized as safe by qualified scientists on the basis of a history of common use in food before 1958 or on the basis of scientific procedures.	Food containing the substance and the substance itself are adulterated if the substance is neither GRAS nor an approved food additive. (A substance that is not GRAS is a food additive.)	No
Unavoidable contaminant	Harmful substance whose addition to food cannot be avoided by good manufacturing practices or is required for production.	Food is adulterated if it contains an unavoidable contaminant in an amount that may render the food injurious to health or if the contaminant exceeds a tolerance set by FDA to protect public health.	No
Animal feed, additive, and drug	Feed, food and color additive, and drug intended for use in animals.	Generally subject to same requirements as similar products for human use; Delaney Clause applies unless the carcinogenic substance does not harm the animal and no residues are detected.	Same as similar product for human use

Source: GAO summary of selected FFDCA provisions and FDA regulations.

Food

FFDCA defines food as (1) articles used for food or drink for people or animals, (2) chewing gum, and (3) articles used for components of any such article. According to FDA, the statutory definition of food includes

articles used in the way that most people use food—primarily for taste, aroma, or nutritive value.[2]

Although industry is primarily responsible for ensuring food safety, FDA regulates the safety of foods, including whole foods, (e.g., fruits, vegetables, grains) under the food adulteration provisions of FFDCA section 402. Under these provisions, whole foods are generally not required to undergo premarket review or approval by FDA but are subject to postmarket surveillance for adulteration. Under section 402(a)(1), which was enacted in 1938, FDA may determine that food is adulterated "if it bears or contains any added poisonous or deleterious substance which may render it injurious to health . . . ." Under this standard, FDA can remove a food item from commerce if there is a reasonable possibility that a substance added by human intervention may be injurious to health. Under section 402(a)(1), FDA may also determine that a food is adulterated if it bears or contains a naturally occurring poisonous or deleterious substance that ordinarily renders it injurious to health. FDA has successfully interpreted this section of FFDCA to mean that any substance that is not naturally occurring in food is an "added" substance and may be regulated under the more stringent standard of "may" render injurious to health. Naturally occurring substances concentrated by human intervention are considered "added" under this section.

A food substance may also be found to be adulterated if it is filthy, is produced under insanitary conditions, or contains unapproved food additives, unapproved color additives, or certain unapproved pesticide residues.[3] Substances added intentionally to accomplish a function in food or otherwise become a component of food may be subject to the premarket review provisions of FFDCA for food and color additives, pesticide residues, and new animal drugs.

To conduct postmarket surveillance, FDA inspects domestic establishments that manufacture, process, pack, or hold food for interstate commerce to ensure compliance with federal laws, regulations, and good manufacturing practices. FDA's good manufacturing practices regulations specify requirements to ensure that food is safe and has been prepared, packed, and handled under sanitary conditions to avoid contaminating or rendering the food injurious to health. Among other things, these

[2]FDA defines nutritive value as a value that sustains human existence by, for example, promoting growth, replacing depleted essential nutrients, or providing energy.

[3]FDA shares responsibility with the Environmental Protection Agency (EPA) for regulating pesticide residues in food. EPA establishes tolerances for pesticide residues that may remain in/on food or feed, and FDA monitors and enforces these limits.

requirements specify generally the kinds of buildings, facilities, equipment, and maintenance that are needed; a building's design and construction, lighting and ventilation; procedures for cleaning equipment; and other facilities and operations. Additional regulations specify requirements for certain types of food products, such as low-acid canned foods. In addition, FDA inspects imported food products at the port of entry to ensure that the products meet the same safety and labeling requirements as domestic foods.

FFDCA prohibits the interstate distribution, including the importation, of articles that are adulterated or misbranded.[4] By law, regulation, and various policies, FDA can take a variety of enforcement actions to handle violations. Among other things, FDA can issue written warnings to violators, request the voluntary recall of violative products, seize adulterated and/or misbranded food, seek court orders to prevent further distribution of adulterated food, and seek criminal prosecutions of firms and individuals responsible for violations.

Food and Color Additives

Concerned about the increased use of chemicals added to food, the Congress, in 1958, amended FFDCA to require premarket review and approval of food additives. Under FFDCA, a food additive is ". . . any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food . . . ." A food additive may be any substance used in producing, processing, or packaging food, including a source of radiation used to treat food. Common food additives include substances added directly to food, such as preservatives, emulsifiers, thickening agents, flavors, and artificial sweeteners, as well as substances that indirectly become components of food, such as packaging materials and sanitizing agents.

The definition of food additives excludes

- substances generally recognized as safe (GRAS);
- substances used in accordance with a sanction or approval granted before FFDCA was amended in 1958 (1) by FDA or (2) by USDA under the Meat Inspection Act, which was enacted in 1907, or under the Poultry Products Inspection Act, which was enacted in 1957 ("prior sanctioned");
- color additives;

[4]Misbranding includes statements, designs, or pictures on labeling that are false or misleading and failure to provide material information on labels.

- new animal drugs; or
- pesticide residues in/on raw agricultural commodities.

In 1960, the Congress amended FFDCA to establish a system of premarket clearance for color additives intended for use in food, drugs, or cosmetics. Color additives are dyes, pigments, or other substances capable of imparting color, excluding those substances that impart color but are intended for other purposes in food. The regulatory requirements and safety standards for color additives are similar to those for food additives.

Whereas FDA bears the burden of proving that a food product is adulterated after the product has entered the market, a manufacturer bears the burden of proving that a food additive's use is safe before the additive may enter the market. Generally, a substance that is a food or color additive cannot be used legally in food or feed unless FDA has established a regulation specifying the conditions under which the additive may be used safely. Food products containing unapproved food or color additives are considered adulterated and are subject to FDA's enforcement action. Although FFDCA does not specifically define safety, an FDA regulation, which is derived from the legislative history of the 1958 Food Additives Amendment, requires manufacturers of food and color additives to demonstrate to a reasonable certainty that consumers will not be harmed as a result of the intended use of an additive. This requirement obliges manufacturers to meet what is considered a relative standard of safety. However, neither the food nor the color additive provisions authorize FDA to weigh the potential benefits against the potential risks of an additive's use. Furthermore, in 1958, the Congress also enacted section 409(c)(3)(A), commonly known as the "Delaney Clause," which established a more stringent or absolute standard of safety for carcinogenic food additives. Once a substance is found to induce cancer in people or animals, no food additive petition for its use may be approved and any already approved use must be banned. Section 706(b)(5)(B) of FFDCA, part of the 1960 amendment, sets out a substantially similar anticancer standard for color additives.

Manufacturers are required to submit a food additive petition to FDA with adequate data, including the results of laboratory animal studies where necessary, to demonstrate that an additive is safe and will accomplish its intended function (i.e., a preservative must preserve). FDA may set tolerance levels (i.e., legal limits) for the use of an additive. In addition, FDA may require, as part of the petition, submission of relevant information about the manufacturing process, including a full description of the

methods used in, and the facilities and controls used for, producing the additive. Generally, under the food additive provisions, FDA regulates the intended use of an additive and not the method by which the additive is produced. If a manufacturing process is not specified in a food additive regulation, manufacturers are free to use any manufacturing process or to change a process to produce the additive without notifying FDA as long as the resulting additive meets all applicable regulatory requirements and does not introduce contaminants that may render the food injurious to health or new substances that would themselves require approval as food additives.

Unlike approvals for new drugs, food additive regulations are not licenses. Once FDA has issued a regulation specifying the uses and conditions of use for a food additive, any company is free to market the additive as long as the additive is in compliance with the regulation and is not patented. In contrast, a new drug approval allows only a specific company to manufacture the drug at a specific location under specific manufacturing conditions.

FDA has issued regulations to prohibit the direct or indirect use in food of some substances, such as cyclamates. In addition, unavoidable contaminants of foods are regulated separately from food additives under FFDCA. Under section 406, FDA may establish tolerances for harmful substances added to food that are required in the production of food or cannot be avoided by good manufacturing practices. Under this provision, for example, FDA has set tolerances in fish for the unavoidable environmental contaminants polychlorinated biphenyls (PCB).

Prior Sanctioned and Generally Recognized as Safe Substances

Two categories of substances are exempt from the food additive provisions of FFDCA and, hence, from premarket review by FDA:

- Prior sanctioned substances are substances used in food in accordance with sanctions or approvals granted by FDA or USDA before 1958.
- Generally recognized as safe (GRAS) substances are substances that "experts qualified by scientific training and experience" have generally recognized as safe when used as intended in food. This recognition may be based on either (1) a history of common use in food before 1958 or (2) scientific evidence for substances introduced after 1958.

A prior sanctioned food substance is subject to the adulteration provisions of FFDCA section 402. To take action against a prior sanctioned substance,

FDA must be able to prove that the substance may render the food injurious to health. A food ingredient that FDA demonstrates is not GRAS is also subject to the adulteration provisions unless FDA approves a food additive petition for its intended use. A food ingredient that is not prior sanctioned or GRAS requires approval by FDA as a food additive before it may be added directly or indirectly to food.

According to FDA, the Congress created the GRAS exemption because it recognized that subjecting every intentional additive to FDA's premarket review was not necessary to protect public health and would impose an unreasonable burden on FDA and the food industry. First, the safety of many food ingredients had already been established before 1958 through the ingredients' long history of safe use in food. Second, the safety of some substances first used in food after 1958 could be determined through scientific procedures by qualified experts without a premarket review by FDA. Thus, many food ingredients derived from natural sources—such as salt, pepper, vinegar, vegetable oil, spices, and natural flavors—as well as many chemical additives—such as some sweeteners, preservatives, and artificial flavors—are legally considered GRAS and not food additives. As such, they may be marketed without having been reviewed by FDA and without being the subject of a food additive regulation. From time to time, FDA has published lists of substances considered GRAS, but no comprehensive list exists. Although the total numbers are not known, FDA estimates that approximately 1,450 of about 2,700 substances that it knows are added directly to food are GRAS and prior sanctioned substances. The majority of these substances have not been reviewed by FDA.

The safety of GRAS substances used for the first time after 1958 must be supported by scientific evidence—ordinarily based on general scientific agreement grounded in published studies. However, the support for these GRAS substances does not have to be submitted to FDA for its review and approval. As noted above, authority for making GRAS designations is not limited to FDA; qualified experts can also review the scientific evidence and independently determine that a food substance is GRAS. For example, the expert panel of the Flavor and Extract Manufacturers' Association has asserted the GRAS status of hundreds of synthetic flavoring chemicals. In addition, following the procedures noted above, manufacturers may determine that a new food ingredient is GRAS and use it to produce a food product without consulting FDA even if FDA has not officially listed the substance as GRAS. However, FDA has the authority to challenge the manufacturer's assessment of GRAS status and ultimately require submission of a food additive petition or take action to stop the marketing

of the product. When challenged, a manufacturer must prove that its food substance is, in fact, GRAS.

FDA has established a procedure through which manufacturers and others may voluntarily petition the agency to review and affirm the GRAS status of substances that directly or indirectly become components of food. GRAS affirmation petitions require the same quality and quantity of data as petitions for food additives, and petitioners must demonstrate that the criteria for GRAS status have been met. If, after evaluating the petition, FDA finds that the substance is GRAS, it must publish a regulation to this effect. If FDA finds that the substance is not GRAS, it must publish a notice that the substance is a food additive subject to the food additive provisions of FFDCA.

In addition, under FDA regulations, a change in the composition of a food ingredient or in the method of manufacture that changes the food substance may ultimately affect the substance's GRAS status. Manufacturers are responsible for determining whether these changes affect the GRAS status of their ingredient.

Animal Feed, Additives, and Drugs

Animal feed, food and color additives, and new drugs intended for animals can affect the safety of animal products eaten by consumers. These substances are generally subject to the same requirements under FFDCA as similar products intended for human use. Animal feed includes commercial feed and feed manufactured on the farm. Like human food, animal feed is subject to FDA's postmarket surveillance for adulteration. Substances added to animal feed, such as preservatives, are subject to the same premarket review requirements as additives for use in human food. Therefore, FDA must approve a food additive regulation for an ingredient in animal feed unless the substance is GRAS or prior sanctioned.

Under section 512 of FFDCA, FDA is responsible for determining whether new animal drugs, such as antibiotics for use in dairy cows, are safe and effective for those animals and whether the food products, such as milk, that are derived from treated animals will be safe for human consumption. Food items containing unapproved and/or excess animal drug residues are adulterated and are subject to enforcement action. Generally, FDA must approve new animal drugs before they may be legally marketed in the United States. Under FFDCA, animal drug companies must submit data to FDA to demonstrate that their products are safe and effective for their intended use(s).

Although new animal drugs are not categorized and regulated as food additives, FFDCA sets out safety standards substantially similar to those specified in the Delaney Clause when these substances are found to induce cancer in people or animals. Carcinogenic animal drugs and feed are, however, exempt from the Delaney Clause's prohibition against use if (1) the substance will not harm the animals for which it is intended and (2) no residues of the substance are found by methods approved by FDA in the animal product reaching the consumer.

New Biotechnology

This appendix describes FDA's regulation of food products derived from new biotechnology. It covers (1) a definition of new biotechnology; (2) examples of the products or applications of the technology; (3) possible food safety concerns; (4) FDA's responses to the technology, especially the agency's policy for regulating genetically engineered plants; and (5) any unresolved regulatory issues.

Definition

In general, biotechnology refers to the use of living organisms or components of organisms, such as enzymes,[1] to produce commercial products and perform industrial processes. The term "biotechnology" can refer to traditional genetic modification, such as cross-breeding, as well as to recently developed methods for manipulating genes, such as recombinant deoxyribonucleic acid (rDNA)[2] and cell fusion,[3] which are sometimes referred to as genetic engineering.

For centuries, people have used biotechnology to manufacture certain foods and food ingredients—such as bread, beer, cheese, and yogurt—and to improve agricultural crops—such as hybrid corn. According to FDA, almost all food crops today have been genetically modified. The terms "genetic engineering" and "new biotechnology" refer in this report to the newer forms of biotechnology developed in the 1970s that directly modify the genetic materials of plants, animals, and microorganisms.

Applications and Examples

Genetic engineering holds the promise of revolutionizing food and agricultural production and processing. It may be able to provide foods that are more nutritious, tasty, and abundant and less expensive than those from traditional sources. According to industry advocates and others, genetic engineering techniques offer a more precise means of creating many food products and processes than traditional biotechnology (e.g., plant breeding). They can also dramatically accelerate the rate of certain biological processes, such as the production of new strains of plants and animals. In addition, genetic engineering has made it possible to transfer genes between very different kinds of organisms—something that

[1]An enzyme is a complex protein that promotes a chemical reaction without itself being changed. Enzymes are added during food processing to affect a product's texture, appearance, and flavor.

[2]rDNA processes refer to recombining or splicing segments of the genetic material, or DNA, of one organism into the DNA of another so that the recombined material is reproducible in the offspring. DNA is the genetic material found in all living organisms.

[3]In cell fusion, two cells are fused together through the use of chemicals or electricity to produce a hybrid cell of novel genetic composition without the transfer of DNA.

is not possible with traditional breeding methods. New techniques, such as rDNA, do not displace traditional plant breeding but can expand and improve on traditional methods.

Modern genetic engineering can be applied in diverse ways to improve existing food products and processes and/or produce novel varieties and methods, including new foods, new food ingredients, new processes to produce existing foods and food additives, and new diagnostic tools.

- Foods: Genetic engineering can be used to develop transgenic organisms—plants, animals, and fish carrying a gene inserted from another organism to enhance a desired trait. For example, plants can be genetically engineered to resist disease, insects, adverse weather conditions, or the effects of a particular herbicide. In addition, organisms can be genetically engineered to improve their processing and marketability—to delay the ripening of fruit, for example, or to extend shelf-life—as well as to improve their nutritional content and flavor. Transgenic animals may be created that will be more resistant to disease or more capable of growth, lactation, and reproduction. Transgenic plants and animals may also be used as live factories to produce nonfood chemicals, such as plastics, vaccines, and pharmaceuticals. Transgenic plants and animals are actively being researched and developed, and a number of transgenic plants—including modified tomatoes, cotton, and soybeans—are expected to enter the marketplace in the near future. According to FDA, more than 30 different agricultural crops developed with rDNA are being tested in field trials.
- Food ingredients: New biotechnology can be used to produce food ingredients—such as ingredients used to sweeten, color, flavor, or modify the texture of a food product—that have previously been produced through conventional methods.
- Food processes: Genetic engineering can be used to improve traditional food processes, such as fermentation for making bread, alcoholic beverages, and cheese. Modern techniques can also be used to develop new and improved enzymes for processing food products. Most of the applications of modern genetic engineering related to food have occurred in the enzyme and fermentation industries to date, according to the Institute of Food Technologists, a scientific association. The enzyme chymosin, for example, which is used in producing cheese and other dairy products, has traditionally been derived from calves' stomachs but can now be obtained by microbial fermentation.
- Diagnostic tools: Genetic probes incorporating molecular biological techniques can be used to quickly identify and screen food contaminated

with toxins (e.g., aflatoxin), pathogenic (disease-causing) organisms (e.g., salmonella), and chemical substances (e.g., illegal residues of antibiotics or pesticides). These screening methods hold great potential for improving food safety.

According to a 1988 FDA study of the current and future state of the U.S food biotechnology industry, genetic engineering was expected to have a major impact on the food industry in the coming decade. The study identified 155 firms applying newer biotechnologies on over 400 research and development projects—almost all of which were thought to be technically feasible before 1992. Genetically engineered soybean, cotton, rice, corn, oilseed rape, sugar beet, tomato, and alfalfa crops are expected to enter the marketplace by the year 2000. Recently, market analysts estimated that sales in the food biotechnology market could reach $10 billion by 2000. In addition, the science of new biotechnology is developing rapidly, as is the scientific knowledge of the risks it may pose.

Food Safety Concerns

Although new biotechnology promises to improve agriculture and food production, controversies exist over the risks that it may pose to human health and the environment. Resolution of these controversies is hindered by scientific limitations in, and lack of scientific consensus on, the ability to evaluate the risks posed by some applications of biotechnology, as well as the ability to detect whether food and food ingredients have been genetically modified or produced through new biotechnology.

Controversy Over Risks From New Biotechnology

Central to the controversy over whether premarket approval should be required for food products developed through new biotechnology is whether the technology is so novel and poses such unique safety consequences that FDA should regulate the process as well as the products of the process.

Many scientists from government, industry, and academia believe that there is no evidence of new or unique hazards associated with new biotechnology. According to these scientists, any risks that may occur are similar to those associated with unmodified organisms or organisms genetically modified by conventional breeding methods. In short, these scientists believe that new biotechnology is an extension of traditional genetic modification techniques and, hence, the foods produced by these techniques do not present any different or greater safety concerns than the foods that Americans currently eat. Supported by this scientific finding,

the federal government has maintained since about 1984, and reaffirmed several times since, that products developed through new biotechnology do not in themselves pose risks to human health or the environment; according to FDA, risk depends on the characteristics and use of the individual products, not on the process by which they are created.

FDA scientists and others also believe that the probability of adverse effects associated with genetic engineering is low if plant breeders exercise the same level of caution as they have with traditional breeding and follow well-established practices to identify and exclude from commercial use plants that exhibit unexpected adverse traits. According to a report by the Office of Technology Assessment (OTA),[4] no evidence has yet demonstrated that the development of new crop varieties has significantly decreased the safety of the food supply. Furthermore, some scientists claim that possible adverse effects can be identified and planned for and therefore pose minimal safety concerns. Some scientists also argue that the risks associated with new biotechnology might be even lower than those associated with traditional methods because these new technologies allow genes to be manipulated more precisely.

Nonetheless, few experts and others believe that applications of new biotechnology to food are totally without risk to human health and the environment, and some urge caution while society develops experience with the technology and learns how to classify and manage any risks associated with it. Consumer and environmental groups believe that genetic engineering is a radical new technology, not an extension of traditional plant breeding. According to these groups, new biotechnology poses new and unique safety risks because it will allow genetic modifications that are not possible with traditional breeding and will permit the introduction of food products that have not previously been a part of the food supply. In addition, comparing the safety of new biotechnology with that of conventional biological methods is not comforting for some people because notable unexpected problems occurred in the past when nonnative organisms were introduced and even when conventional breeding techniques were used. The gypsy moth, for example, defoliated trees, and a potato modified through traditional cross-breeding produced toxic levels of solanine (an alkaloid). Consumer and environmental groups fear even the rare occurrence of unexpected events because they believe that new biotechnology may have greater potential for harm than previous technologies. Mistakes caused by new

[4]U.S. Congress, Office of Technology Assessment, A New Technological Era for American Agriculture, OTA-F-474 (Washington, D.C.: Aug. 1992).

biotechnology may have a greater impact than earlier mistakes because they may be introduced faster and may expose more of the population and the environment. These groups also point out that, historically, society has always demanded greater assurances of safety for food products altered by people than for those occurring naturally.

The following are some of the food safety concerns that various commentators have indicated are at least theoretically possible with new biotechnology:[5]

- the production of unexpected effects, including multiple effects resulting from a single genetic change ("pleiotropic" effects), of potential health significance;
- an increase in levels of naturally occurring toxins and allergens or the activation of dormant toxins or allergens;[6]
- the introduction of known or new substances that may be toxins, allergens, or antinutrients;
- an adverse change in the composition, absorption, or metabolism of important nutrients;
- a reduction in the effectiveness of some antibiotics through the use of antibiotic-resistant marker genes (discussed below);
- the production of adverse environmental consequences, including harmful effects on wildlife and ecosystems;
- an adverse change in the quality and nutritional sufficiency of animal feed or an increase in the level of toxins in plant byproducts fed to animals.

These risks are more uncertain and, therefore, of greater concern if the gene used in producing the food is derived from a pathogenic microorganism or has never been a component in food. There is also some concern that adverse effects may occur in subsequent generations of genetically engineered plants and animals.

L-tryptophan: Consumer and environmental groups have frequently cited an incident involving L-tryptophan as a possible example of genetic engineering gone awry. L-tryptophan is an amino acid that was sold as a

[5]See FDA's "Statement of Policy: Foods Derived from New Plant Varieties," Federal Register Vol. 57, No. 104 (May 29, 1992), p. 22984; Field Testing Genetically Modified Organisms: Framework for Decisions, National Research Council (Washington, D.C.: National Academy Press, 1989); International Food Biotechnology Council, "Biotechnologies and Food: Assuring the Safety of Foods Produced by Genetic Modification," Regulatory Toxicology and Pharmacology, Vol. 12, No. 3 (Dec. 1990); and Environmental Defense Fund, A Mutable Feast: Assuring Food Safety in the Era of Genetic Engineering (New York, N.Y.: Oct. 1, 1991).

[6]An allergen is a substance that causes allergic reactions in humans.

dietary supplement to treat insomnia and depression. Produced by a Japanese company using genetic engineering, the supplement was linked through epidemiological data to an outbreak in 1989 of eosinophilia-myalgia syndrome (EMS), a rare blood disorder that causes severe muscle pain, neurological damage, and, in some cases, death. The outbreak has been linked to at least 1,500 illnesses and 38 deaths, and many cases have gone undiagnosed, according to the Centers for Disease Control and Prevention. Since November 1989, FDA has issued several consumer and import alerts and manufacturers have recalled L-tryptophan products—effectively removing most of these products from the market in the United States. Although the exact cause of the illnesses has not been determined, FDA officials do not believe that the L-tryptophan problem was due to genetic engineering, but they cannot rule out the possibility at this time.

Scientific Limitations Hindering Resolution of Uncertainty Over Risks

Current limitations in science hinder the resolution of uncertainties over the risks posed by food and food ingredients derived from new biotechnology. These limitations also stand in the way of resolving the debate over how to regulate these products.

Much of the concern over food safety risks that may accompany new biotechnology center on science's current inability to predict unexpected effects that may occur from manipulating genes. Scientists do not agree on whether the risks from new biotechnologies can be assessed in the same manner as the risks from genetic modifications obtained through traditional methods of breeding. According to some scientists, no generally acceptable scientific procedures can routinely be applied to evaluate the safety of whole foods. Traditional approaches to food safety assessment, such as classical toxicological tests on laboratory animals, are inadequate because studies that examine the biological effects of exaggerated doses of single chemicals in animals do not work well for foods that consist of complex chemical mixtures. According to some scientists, human studies may be necessary to assess the potential effects of new substances that replace or displace major dietary components or of products whose nutritional and functional characteristics have been modified.

Some scientists believe that the safety of genetically engineered food can be assessed by comparing a new food item with its traditional counterpart and observing any significant differences. However, food scientists also recognize that knowledge of the characteristics of food and nutrients and

of their appropriate percentage in the human diet is limited—including knowledge of the possible effects of long-term exposure to naturally occurring toxins—and that more research is needed. Without adequate knowledge of an existing food component's characteristics and effects and of any changes that may occur during processing or cooking, it may be difficult to assess the effects of genetic engineering. FDA officials note, however, that, at least initially, most products produced through new biotechnology will exhibit relatively incremental modifications whose effects can be assessed by standard molecular, chemical, and toxicological methods.

The potential for allergenic effects is a concern that is difficult to test scientifically. Many foods, such as milk, eggs, wheat, fish, and peanuts, commonly cause allergic reactions in some people. Recent reports in the medical literature indicate that although the number of people who experience allergic reactions to food is unknown, up to 8 percent of children and 2 percent of adults may suffer from food allergies. The authors of these reports believe that recent increases in the incidence of severe allergic reactions to food, including death, may be due to the increased use of protein additives in commercially prepared foods.[7] (Almost all known food allergens are proteins.) According to the Biotechnology Strategic Manager in FDA's Center for Food Safety and Applied Nutrition (CFSAN), it is unlikely that a food protein present at trace levels with no prior history of allergenicity would produce allergic reactions in people after being inserted into a food item. However, FDA acknowledges that it is "unaware of any practical method to predict or assess the potential for new proteins in food to induce allergenicity . . . ." Consumer and environmental groups are concerned about the potential for novel proteins to cause allergic reactions in people.

Scientists currently lack an analytical method to detect whether a food or food ingredient has been produced or genetically modified through new biotechnology. Furthermore, scientists disagree on whether such a method can be developed, especially for food products comprising complex mixtures. This scientific limitation may have significant implications for enforcing food laws and regulations as well as for screening imported products to determine compliance.

Several representatives from industry, government, academia, and public interest groups have suggested that FDA convene scientific advisory panels

[7]Hugh A. Sampson, et al., "Fatal and Near-Fatal Anaphylactic Reactions to Food in Children and Adolescents," The New England Journal of Medicine, Vol. 327, No. 6 (Aug. 6, 1992), pp. 380-384.

to help resolve some of the questions concerning the safety of genetically engineered food products, especially questions concerning food allergens and analytical methods for monitoring. CFSAN's Biotechnology Strategic Manager agrees that FDA will need to do more work in some areas, including the area of allergens. FDA plans to announce soon how it will obtain scientific advice on the potential for genetically engineered food to cause food allergies.

FDA's Responses

FDA has responded to new foods and food ingredients produced through new biotechnology in several ways.[8] These responses include (1) developing a regulatory approach, (2) reviewing/approving certain products, (3) creating new offices and positions, and (4) sponsoring/conducting studies and symposiums on biotechnology. As part of its mandate to ensure food safety, FDA has taken other actions that have also affected its ability to respond to genetically engineered food products, such as creating the National Center for Food Safety and Technology. These and other actions that cut across individual technologies are discussed in appendix VI.

Regulatory Approach

No particular statutory provision or regulation deals explicitly with food and food ingredients produced or genetically modified through new biotechnology. However, on May 29, 1992, FDA published a policy statement explaining how it would regulate foods and animal feed derived from new plant varieties, including plants developed through new genetic modification techniques, such as rDNA.[9] Under this policy, FDA intends to regulate the new fruits, vegetables, and grains and their byproducts developed through new biotechnology within the existing regulatory framework of FFDCA and FDA regulations that apply to all existing food products under its jurisdiction. FDA believes that it has adequate legislative authority to ensure the safety of all food products, including those produced through new biotechnology, and that no new laws are necessary.

FDA intends to apply the existing regulatory framework for food and food ingredients to regulate the food products developed through new biotechnology. (See app. I for a description of this regulatory framework.)

[8]This report focuses on FDA's responses that are related directly to food safety and does not include FDA's responses that are related to environmental concerns and may be required under the National Environmental Policy Act.

[9]Food and Drug Administration, "Statement of Policy: Foods Derived From New Plant Varieties," Federal Register, Vol. 57, No. 104 (May 29, 1992), p. 22984.

Thus, FDA will regulate most plant foods—especially whole foods (e.g., fruits, vegetables, and grains)—derived from genetically modified plants under the postmarket adulteration provisions of FFDCA, which serve as FDA's primary means to ensure the safety of most of the U.S. food supply. Like previously introduced whole food derived from plants modified by traditional cross-breeding, genetically engineered whole food will not require premarket review. According to CFSAN's Biotechnology Strategic Manager, FDA will regulate any unintended or unexpected effects that may occur as a result of genetically modifying plants under the postmarket adulteration provisions of FFDCA. If, for example, FDA finds that a genetically engineered plant, such as a new variety of tomato, contains a higher-than-intended level of a naturally occurring toxin or contains an unexpectedly harmful substance that may render the food injurious to health, FDA could declare the food item adulterated and in violation of FFDCA. According to FDA, FFDCA places a legal duty on companies to ensure that the foods they market are safe and in compliance with applicable legal requirements. Although FFDCA does not require premarket approval of new foods, FDA has encouraged firms developing new food crops to discuss with FDA the scientific information on which safety claims will be based before marketing the food item.

Under FDA's policy, a substance that is intended or expected to become a component of food through genetic engineering (i.e., a transferred gene and the traits it may express—called expression products) could be subject to premarket review as a food additive unless the substance is generally recognized as safe (GRAS) or otherwise exempt from regulation as a food additive. According to FDA officials, a substance that would be a food additive if it were added during traditional food manufacture would also be a food additive if it were introduced into food through the genetic modification of a plant crop. Thus, if a genetically engineered substance does not differ substantially from a food substance that has a history of safe use or has been designated GRAS, it may be considered GRAS and exempt from FDA's premarket review. However, if a genetically engineered substance differs significantly in structure, function, or composition from substances currently found in food or if it otherwise raises a safety question (e.g., has no history of safe use in food), it may not be considered GRAS and may require FDA's premarket approval as a food additive. For example, FDA would probably regulate as a food additive a novel sweetener that was added to food by genetically modifying a plant crop. According to FDA, substances intentionally introduced into food that would be reviewed as food additives include those that have unusual chemical functions or known toxicity, those that are major dietary components of

food, or those whose safety is uncertain. In addition, under the biotechnology policy, a GRAS substance produced or modified through new biotechnology may lose its GRAS status if the substance has been significantly altered. The substance would then be classified and regulated as a food additive. However, FDA has not explicitly defined significant difference or alteration in either its policy or its regulations.

For a new substance added to food through genetic engineering, as for substances added to food through traditional methods, the manufacturer must determine whether the substance falls within the scope of an existing food additive regulation, requires a new food additive regulation, or is exempt from regulation as a food additive because it is GRAS. Of course, FDA could challenge the manufacturer's determination.

In its policy statement, FDA also announced that foods derived from or modified by new biotechnology would be labeled, like all existing foods, on the basis of their composition. FDA is not requiring special labeling for genetically engineered food because it does not believe that this information about the food's origin/method of manufacture needs to be conveyed to consumers on a food label. In the past, FDA generally has not required food labeling to inform consumers and users that new plant varieties, such as hybrid corn, were derived from traditional cross-breeding and other genetic modification techniques. FDA does not believe that new biotechnologies justify a change in its labeling policy, but the agency is obtaining further public comment on this issue (see next section).

FDA will, however, require that a genetically engineered food product be labeled to inform consumers if the new product differs significantly in composition or identity from its traditional counterpart. For example, labeling will be required if a new, genetically engineered tomato contains no vitamin C. FDA will also require that genetically engineered food products be labeled if consumers need to be alerted for safety reasons. For example, FDA has stated that it will require labeling if a gene from a commonly allergenic food is introduced into a food that was not previously considered allergenic unless the manufacturer can demonstrate that the gene transfer will not cause allergic reactions in humans. Thus, according to FDA, tomatoes bred to contain a peanut protein would need to be labeled to disclose the presence of the peanut protein unless the manufacturer could conclusively demonstrate that the new tomato did not cause allergies in people allergic to peanuts. Under FDA's policy, proteins

taken from commonly allergenic foods are presumed to be allergens unless demonstrated otherwise.

FDA's policy statement contains a series of flow charts to guide industry in assessing the safety, nutritional value, and regulatory status of foods developed through new biotechnology. In particular, these charts are designed to show when circumstances may trigger a premarket review by FDA. FDA recognizes that, for many applications of new biotechnology, the appropriate regulatory category may not be clear; therefore, the agency encourages manufacturers to consult with it to resolve any safety or regulatory issue before marketing a new food or food ingredient.

FDA's policy statement follows the guidance established by the Office of Science and Technology Policy in February 1992. According to this guidance, the federal government's regulatory oversight should focus on the characteristics and risks of the biotechnology product—not on the process by which it is created. FDA may, however, consider the manufacturing process in its review of some new products to help understand the safety or nutritional characteristics of the end product, according to FDA officials. FDA's policy statement is also consistent with the scientific conclusions and recommendations of expert panels from the National Academy of Sciences, the International Food Biotechnology Council,[10] and several international organizations.

FDA's biotechnology policy does not cover foods and food ingredients derived from algae, microorganisms, and other nonplant organisms; animals; or fish. The policy statement also does not apply to new animal drugs or pesticides. FDA has some experience with microorganisms and new animal drugs developed through new biotechnology, as explained in the following section. In addition, according to CFSAN's Biotechnology Strategic Manager, FDA may consider developing regulatory guidelines for animal products under its jurisdiction, including fish, at some later date.

FDA's policy is, to some extent, still evolving. FDA invited public comment on its policy, especially on the types of compositional changes that might be considered significant in determining when premarket review would be necessary and on the requirements for labeling foods developed through new biotechnology. According to CFSAN's Biotechnology Strategic Manager, FDA has been reviewing the comments it received on the policy statement to identify issues that require more work. For example, in

[10]The International Food Biotechnology Council is an association of about 30 large food-producing firms and small biotechnology companies.

response to the comments it received concerning the labeling of genetically engineered food, FDA published a Federal Register notice in April 1993 requesting additional data and information on the issue.[11] FDA plans to hold a public hearing on the issue after it has reviewed the new comments it receives. (See the discussion of unresolved issues in the next major section.)

Product Review and Approvals

To date, few food products developed through new biotechnology have been submitted to FDA for premarket review and approval. Since 1984, FDA has received (1) seven petitions to affirm the GRAS status of substances produced through new biotechnology, (2) two requests for advisory opinions, and (3) two food additive petitions. FDA has affirmed three GRAS petitions for the use of a genetically engineered enzyme and is reviewing the remaining petitions and requests.

On March 23, 1990, FDA affirmed the GRAS status of chymosin produced by genetically altered bacteria. Chymosin, also known as rennin, is an enzyme used in milk culturing that is traditionally derived from the stomachs of calves. This was the first genetically engineered food product approved by the agency. FDA determined that the genetically engineered enzyme was identical to the naturally occurring enzyme that had been classified as a GRAS substance in 1983 and that the new manufacturing process did not introduce any unsafe impurities. FDA said that this petition review was a learning experience for the agency and helped it to identify the questions and data needed to assess the safety of such products. FDA's review of the GRAS affirmation petition for chymosin took about 2.5 years.

On May 1, 1991, FDA published a notice in the Federal Register seeking public comment on a request for FDA to issue an advisory opinion on the use of the kanamycin resistance gene as a "selectable marker" in genetically modified plant crops, including tomatoes. This gene allows plant cells to survive exposure to the antibiotic kanamycin. By physically linking the kanamycin resistance gene to another gene that specifies a desired trait, scientists can select plant cells that have successfully incorporated the desired trait by selecting the cells that survive exposure to kanamycin. FDA chose the advisory opinion route because (1) a number of companies used the gene, (2) the use of the substance raised a broad policy issue concerning how the agency should regulate agricultural crops (whole foods) produced through new biotechnology, (3) the request did

[11]Food and Drug Administration, "Food Labeling: Foods Derived From New Plant Varieties," Federal Register Vol. 58, No. 80 (Apr. 28, 1993), p. 25837.

not pertain to the approval of a food or food ingredient, and (4) the advisory opinion was in the public interest because the process was open to public comment and scrutiny. In January 1993, the manufacturer requested that FDA convert its request for an advisory opinion to a food additive petition. FDA is also reviewing a food additive petition for a genetically engineered enzyme used as a processing aid in brewing alcohol.

In August 1991, FDA received a request for an advisory opinion to declare a genetically engineered tomato a "food." A California-based company genetically engineered a tomato to delay ripening and softening and thereby extend shelf life. The company did not believe that FDA's premarket approval was necessary to sell the modified tomato but thought that an FDA opinion would help the company convince consumers that the tomato was safe to eat. On May 29, 1992, the same day that FDA announced its biotechnology policy, the agency published a notice in the Federal Register seeking comments on whether the genetically engineered tomato could be considered a food and therefore subject to the same regulations as other tomato varieties developed through traditional cross-breeding techniques. FDA had delayed publication of the notice pending completion of its policy statement on foods developed through biotechnology. FDA expects that future requests for consultation with FDA on such matters will follow the guidelines set forth in FDA's policy statement. In other words, FDA does not expect to use advisory opinions to resolve safety and regulatory questions concerning genetically engineered food in the future. The genetically altered tomato is expected to be marketed following FDA's decision on the use of the kanamycin resistance gene as a food additive in the tomato.

FDA's Center for Veterinary Medicine (CVM) has been reviewing applications for new animal drugs developed through new biotechnology. For example, CVM has been reviewing both a bovine growth hormone developed to increase milk production, called bovine somatotropin (BST) or recombinant bovine growth hormone (rBGH), and a porcine growth hormone designed to promote weight gain, increase feed efficiency, and produce leaner meat. The proposed use of rBGH and FDA's review of it have been controversial.[12]

[12]As of May 1993, FDA was considering whether to approve the use of BST. See also Recombinant Bovine Growth Hormone: FDA Approval Should Be Withheld Until the Mastitis Issue Is Resolved (GAO/PEMD-92-26, Aug. 6, 1992).

Organizational Changes

FDA has made several organizational changes in response to new biotechnology. In 1986, FDA created a Biotechnology Coordinator within CFSAN to answer questions surrounding food biotechnology within CFSAN, develop policies and guidelines, and serve as the liaison to other FDA units and to external groups. In 1989, FDA created the Office of Biotechnology to coordinate agencywide biotechnology issues and to represent FDA in interagency meetings. The head of this office chairs the FDA Biotechnology Coordinating Committee, which consists of representatives from each FDA center and other units.

In 1989, FDA's Office of Regulatory Affairs created a multipurpose biotechnology laboratory in Dallas, Texas, with specialized expertise to inspect various manufacturing firms, analyze regulatory samples, and perform research in biotechnology. This office plans to use the laboratory as its technical resource for analyzing food products derived, wholly or partially, from biotechnology.

More recently, FDA has reorganized its Center for Food Safety and Applied Nutrition (see app. VI). As part of this reorganization, the Biotechnology Coordinator became the Biotechnology Strategic Manager responsible for cross-cutting policy issues, long-range initiatives, and planning for foods developed through new biotechnology.

Studies and Communications

FDA has undertaken several studies to develop, and has conducted several activities to communicate, its position regarding the safety and regulatory issues presented by genetically engineered food. In 1987, CFSAN surveyed the food biotechnology industry to identify the companies developing genetically engineered food products and the potential volume and type of products and processes that might confront CFSAN's staff. FDA conducted a similar effort for veterinary products derived from biotechnology in 1986. In 1988, FDA jointly sponsored with USDA and the Environmental Protection Agency (EPA) a scientific conference on the safety and regulatory issues associated with transgenic plants.

FDA officials have published several articles in various scientific and policy journals on the safety and regulatory issues associated with food and food ingredients developed through biotechnology. FDA officials have also held several meetings with consumer and environmental groups as well as with members of industry concerning the agency's biotechnology policy. FDA officials have participated in several international conferences and discussed food biotechnology issues with international organizations, such

as the World Health Organization/Food and Agriculture Organization and the Organization for Economic Cooperation and Development.

Unresolved Regulatory Issues

As of April 1993, FDA had received over 3,300 comments on its biotechnology policy. These comments indicate that reaction has been mixed. Generally, the food industry and biotechnology companies have responded favorably. However, consumer and environmental groups generally believe that the agency's approach does not adequately protect public health or the environment. These groups would prefer that FDA (1) regulate genetically engineered foods under the food additive provisions of FFDCA and require premarket safety testing, (2) require manufacturers to notify FDA before marketing all genetically engineered food substances (establish a mandatory premarket notification system), and (3) require labeling of all genetically engineered foods. Some groups, which oppose genetically engineered food for ethical, moral, religious, scientific, or other unspecified reasons, have threatened legal action to prevent the implementation of FDA's policy. At least one consumer group is organizing an international consumer boycott of genetically engineered foods to prevent the marketing of these new products.

The comments on FDA's policy statement point to several unresolved regulatory issues associated with genetically engineered food. These issues include

- questions about whether the existing regulatory framework for food and food ingredients, established many years before the advent of new biotechnology, provides the most appropriate framework for protecting consumers and facilitating innovation;
- old questions about the adequacy of the regulatory framework for food and food ingredients;
- controversies about approaches other than FDA's for regulating genetically engineered food products;
- controversies about whether genetically engineered food should be labeled; and
- a debate over the proper balance between restraining government regulation and giving the government authority to oversee the food industry.

Adequacy of Existing Regulatory Framework Questioned

According to FDA officials, neither FFDCA nor its legislative history specifically address how FDA should treat food derived from new plant varieties. As previously mentioned, FFDCA does not provide for premarket

approval of new food crops, such as new varieties of tomatoes and corn. In addition, FDA does not have a mechanism to identify, review, or approve foods derived from new food crops before these foods are marketed.

According to CFSAN's Biotechnology Strategic Manager, most staple foods and fermented foods, as well as many traditional food-processing enzymes, predate the establishment of federal food safety laws and have traditionally been considered GRAS without having formally been designated as such because they had a long history of safe use before 1958. Furthermore, according to FDA, when the Congress enacted the food additive provisions in 1958, it did not explicitly consider imposing the premarket approval requirements on new varieties of food crops. Consequently, FDA has generally considered as GRAS food derived after 1958 from new plant varieties that have been genetically modified through traditional cross-breeding. FDA has not found it necessary to conduct premarket reviews of new plant varieties because (1) the genetically modified plants did not generally introduce substances that were significantly different from substances already found in food crops on the market before 1958 and (2) the new food crops, with some exceptions, did not generally cause safety problems. FDA regulations do state that the agency may review the GRAS status of food or food substances of natural biological origin that have been significantly altered by breeding and selection. However, FDA's regulations do not define significant alteration. Thus, FDA has historically relied on postmarket surveillance to oversee the safety of new food crops developed after 1958.

Consumer and environmental groups maintain that FDA's approach fails to protect public health because, in their view, (1) genetic engineering poses unique safety risks and therefore warrants premarket testing and review, (2) FDA's policy allows manufacturers too much discretion in determining the safety of new food products before marketing them, and (3) postmarket surveillance of genetically engineered food will not prevent harm to consumers if things go wrong.

Consequently, according to consumer and environmental groups, FDA should consider transferred genetic material and the results of such transfer (i.e., expression products) to be intentionally added components of food and subject to the premarket approval requirements of FFDCA's food additive provisions. These groups believe that genetic engineering, which was developed after the Congress enacted the Food Additives Amendment in 1958, can affect the composition, efficacy, stability, and safety of food products. To these groups, the legislative history of FFDCA

suggests that the Congress intended to prohibit the marketing of any new food substance that has not been proven scientifically to be safe for human consumption. Hence, according to these groups, manufacturers should be required, before marketing their products, formally to affirm the status of substances they have determined are GRAS.

Consumer and environmental groups are also concerned that under FDA's policy, manufacturers are responsible for initially determining whether their new products are safe and therefore whether they require premarket approval or special labeling. In addition, these groups have criticized the agency for not explicitly defining how a substance would "differ substantially" enough from an approved substance to trigger a premarket review. According to these groups, manufacturers may determine that their products are safe without informing FDA of their determination or publishing the results of their scientific studies for peer review and public scrutiny. In fact, some groups believe that FDA's biotechnology policy liberalizes the GRAS self-determination process because manufacturers may use their proprietary data to determine that their genetically engineered food products are GRAS and do not have to use the publicly available scientific data that are usually required to support the GRAS status of new chemical additives. Because certain manufacturers have not disclosed negative data about such products as silicon breast implants, certain animal drugs, and pesticides, consumer and environmental groups fear that FDA's policy may allow manufacturers too much discretion in determining the safety of, and extent of premarket review required for, their new food products. Consumer and environmental groups believe that the safety of genetically engineered food should be determined either (1) by a federal agency that has no financial interest in the outcome and is accountable to the public or (2) on the basis of a body of publicly available scientific data.

Consumer and environmental groups believe that reliance by FDA on postmarket surveillance of industry determinations of safety is not adequate to protect consumers. First, although FDA can remove adulterated food from the marketplace, it is not likely to do so unless a problem has occurred. Because companies may market their genetically engineered food products without informing FDA, the agency may not know about a genetically engineered food substance until it is consumed and causes harm to consumers. Ultimately, removing an unsafe genetically engineered food product from the market may damage consumers' acceptance of food produced by this new technology. Second, according to consumer and environmental groups, FDA should not bear the burden of

demonstrating that genetically engineered food products are adulterated but rather manufacturers should bear the burden of demonstrating that these products are safe before marketing them.

FDA officials and others believe that requiring all genetically engineered food to be subject to premarket approval is unwarranted and inequitable. FDA bases its policy on its scientific judgment that many of the substances expected to become components of food through the use of genetically modified plants that are approaching commercialization or under development in agricultural research will be the same as, or substantially similar to, substances commonly found in food, such as proteins, carbohydrates, and fats. According to FDA officials, these substances are not known to be toxic and do not raise safety concerns that would require premarket approval. (FDA officials explained the scientific principles supporting the agency's policy in an issue of Science.)[13] In addition, breeders introduce hundreds of new varieties of food plants, animals, and microorganisms into commerce every year without obtaining prior approval from FDA and usually without raising safety concerns, according to FDA. Subjecting all genetically engineered food to premarket review would impose a stricter safety standard on these products than on products developed through traditional breeding and place an undue burden on industry and FDA without increasing consumers' safety. Furthermore, FDA officials note that the agency's policy does not give manufacturers any more discretion in determining the safety and regulatory status of their genetically engineered food products than they currently have for determining the safety and regulatory status of food products developed through traditional methods. FDA officials believe that the same standards for determining the GRAS status of food products should be applied to all food products that pose the same relative risk, regardless of the method of production.

Controversies Over FDA's Policy Reviving Old Questions

The controversies over FDA's policy on biotechnology are reviving old questions about the adequacy of the existing regulatory framework for food and food ingredients. For example, we and others have questioned whether a history of safe use is a viable criterion for accepting new food items.[14] Substances once thought to be "safe" might not be found acceptable today if they were evaluated against modern scientific procedures and standards. In the past, others have argued that the process

[13]David A. Kessler, et al., "The Safety of Foods Developed by Biotechnology," Science, Vol. 256 (June 26, 1992).

[14]See Need for More Effective Regulation of Direct Additives to Food (GAO/HRD-80-90, Aug. 14, 1980).

for self-determining GRAS status needs to be formalized to improve protection for consumers and to give industry a suitable framework for making sound marketing decisions and thereby avoiding an FDA challenge. In addition, some have suggested that all food substances be regulated uniformly. In 1979, the National Academy of Sciences concluded, in part, that the statutory categorization of foods and food ingredients is confusing, cumbersome, and not always clearly related to risks.[15] Among other things, the Academy recommended that the Congress

- abolish the differences in the statutory standards among categories of food substances and create a single standard of risk applicable to all food substances with several broadly defined risk categories (e.g., high, moderate, low);
- authorize interim regulatory actions for a specified time, for substances of uncertain risk, until a substance can be assigned to an appropriate risk category;
- consider an assessment of the benefits of food substances, including physical, psychological, and economic factors; and
- provide FDA with discretionary authority to employ a greater variety of regulatory and educational approaches that encourage or require efforts to develop new technologies to reduce risks and involve consumers in food safety decisions, such as requiring standard symbols or logos for each risk category to alert consumers to the need for further information.

Legislative consideration of these and other changes to the statutory categories and safety standards for food substances have been controversial, as illustrated by the continuing debate over revising the Delaney Clause as it affects pesticide residues in food. Consensus on revising FFDCA has proven difficult to achieve.

Other Proposed Regulatory Options Controversial

Several individuals and organizations have suggested alternatives to FDA's approach for regulating food and food ingredients developed through genetic engineering. However, these, too, have provoked controversy. For example, in December 1990, the International Food Biotechnology Council proposed an approach that closely parallels the approach that FDA later adopted, namely, that genetically engineered food plants and microorganisms be regulated under existing law on the basis of their

[15]Food Safety Policy: Scientific and Societal Considerations. Part 2, Committee for a Study on Saccharin and Food Safety Policy, Institute of Medicine and the National Research Council/Assembly of Life Sciences, National Academy of Sciences (Washington, D.C.: National Technical Information Service, Mar. 1, 1979).

intended use.[16] Consumer and environmental groups have criticized the council's proposal because they believe that regulating only the intended use of the genetic modification would not comply with the premarket testing requirements of FFDCA's food additive provisions.

One regulatory option that various commentators have proposed and debated is a premarket notification or registration system. Although specific proposals differ, such a system would generally require manufacturers to notify FDA before they marketed a food or food ingredient developed through new biotechnology. In principle, such a system would bridge the gap between the absence of a requirement for premarket approval of whole foods and of substances that manufacturers and others have determined are GRAS and the requirement for extensive premarket review of new food additives. Several premarket notification systems have been proposed that range in formality and complexity from relatively simple letters from food companies to notify FDA about the introduction of a new product to mandatory FDA premarket reviews of data submitted by manufacturers to support the safety and/or GRAS status of their food product. For example, the International Food Biotechnology Council has recommended that FDA consider establishing a flexible, voluntary premarket notification system for companies to inform the agency about applications of new biotechnology that might not require formal FDA review and approval. Consumer and environmental groups believe, however, that a notification system should be mandatory and that FDA should maintain a complete list of all food developed through new biotechnology. Furthermore, others, such as OTA, have suggested that a formal notification system should be open for public comment to help alleviate consumers' apprehension about food developed through new biotechnology, especially in the early years of this new technology. FDA officials have considered an expedited review or notification process to augment the current food additive and GRAS affirmation petition processes. Although FDA officials told us during our review that they would like to know what manufacturing process was used to produce new products without regulating the process per se, the agency's policy statement did not require premarket notification of food developed through new biotechnology.

Proponents argue that a premarket notification system offers certain advantages.

[16]International Food Biotechnology Council, "Biotechnologies and Food: Assuring the Safety of Foods Produced by Genetic Modification," Regulatory Toxicology and Pharmacology, Vol. 12, No. 3 (Dec. 1990).

- Improved premarket assurance of safety. FDA would know that food had been genetically engineered before it entered the marketplace and would have an opportunity to determine whether further premarket safety testing and review were necessary to protect public health without unduly inhibiting innovation. In addition, manufacturers would be responsible for demonstrating the safety of their products in a public forum before marketing them. Proponents believe that this responsibility would not unduly burden industry because, under FDA's policy, manufacturers are supposed to have developed a database supporting the safety of their products even if they do not submit the data to FDA. Proponents also point out that Great Britain has adopted a voluntary notification system and Canada has proposed a mandatory system for novel foods and processes.
- Improved postmarket surveillance. FDA field offices would be better able to monitor genetically engineered food introduced into the marketplace (both domestic and imported) and target limited resources to inspecting the food substances that appeared to present the greatest risk. This system might also help FDA track down and remove unsafe products from the marketplace.
- Improved introduction of new products/technologies. A premarket notification system could increase public confidence in the adequacy of FDA's oversight without overburdening industry. Such a system might help allay consumers' fears about biotechnology and promote consumers' acceptance of this new technology. Some assert that a notification system that was open for public comment would help educate the public about the safety of new products and thus foster consumers' acceptance of these products.

Opponents argue that a premarket notification system holds certain disadvantages.

- Extent of premarket approval uncertain. Critics and some FDA officials are concerned that premarket notification does not mean premarket approval and, therefore, the nature and extent of FDA's premarket review would be uncertain. FDA officials are concerned that consumers might not be aware of this difference and could be misled. As a result, some critics are concerned that ultimately FDA would require the same quantity and quality of data for a notice as for a food additive petition in order to avoid misleading the public. In addition, some critics have noted that there is no consensus on the decision criteria or rules for determining when notification would be required (e.g., the level of change that would trigger a notice).

- Increased strain on limited FDA resources. No matter how much review was required under a premarket notification system, any increase in FDA's responsibilities without a concomitant increase in funding for the agency would further strain its already limited resources, according to critics. FDA officials believe that the low risk of most genetically engineered modifications would not justify the expenditures required to operate a premarket notification system for all new genetically engineered food products. FDA might charge food manufacturers to help offset the costs of a premarket notification system; however, we have not analyzed the costs and benefits of a premarket notification system financed by user fees (see app. VI).
- Regulatory overkill. Several opponents believe that a premarket notification system would amount to regulatory overkill because, in their view, genetically engineered food is no riskier than food genetically modified by traditional means. These critics believe that this unnecessary regulation would hinder innovation and American competitiveness in a global economy. However, as OTA has observed, such a system "may be the price industry must pay to have their products accepted by the public, at least in the initial stages of commercializing biotechnology food products."[17]
- Sufficiency of statutory authority questioned. Several critics have questioned whether FDA has the statutory authority to establish a premarket notification system. Consumer and environmental groups believe that FDA could establish a premarket notification system by requiring companies wishing to market genetically engineered foods to file either a GRAS affirmation or a food additive petition. However, as explained above, FDA does not believe that the legislative history of the Food Additives Amendment supports this approach. Furthermore, FFDCA does not provide explicit authority for FDA to establish such a system, according to an FDA attorney. The agency might, however, be able to construct a legal theory to support a premarket notification system under the general provisions of FFDCA if it considered such a system necessary to protect public health. Amending FFDCA to provide explicit authority for a premarket notification system might be necessary to avert potential legal challenges.

In its latest report on new agricultural technologies, OTA presented several policy options for the Congress and FDA to consider in regulating genetically engineered food. OTA recommended, among other things, that the Congress hold hearings on FDA's policy to provide guidance and

[17]Office of Technology Assessment, A New Technological Era for American Agriculture, OTA-F-474 (Washington, D.C.: Aug. 1992).

direction and explore other regulatory options, such as establishing a premarket notification system.

Labeling Genetically Engineered Food Controversial

One of the most controversial issues regarding FDA's policy is whether and when genetically engineered food should be labeled. Critics of FDA's policy believe that all genetically engineered food, should, like irradiated food, be labeled so that consumers can identify and avoid it if they choose. These critics believe that consumers have a right to know whether food has been genetically engineered. They argue that, without labeling, consumers will be misled because they may be unable to distinguish between genetically engineered and other food on the basis of sight, smell, feel, or taste. For example, identifying the presence of animal genes in plants may be important for individuals on diets restricted for religious, philosophical, or other reasons. In developing its policy, FDA tentatively concluded that in the few cases in which an animal gene was inserted into a plant, the characteristics of the plant food would not change in a manner relevant to religious or ethical beliefs.

Most concern about labeling has focused on whether consumers who suffer from food allergies would be sufficiently informed about transferred proteins to avoid food items that could prove to be allergenic. Critics have argued that FDA's policy inadequately protects consumers because manufacturers are initially responsible for deciding whether a label is necessary.

FDA's preliminary analysis of comments on the biotechnology policy indicate that consumers generally want genetically engineered food to be labeled. This finding is consistent with research conducted by USDA and others. However, some research also indicates that consumers may not be willing to pay much for the labeling. Some growers also want genetically engineered varieties to be labeled to distinguish them from nongenetically engineered varieties because they fear that consumers may not accept certain genetically engineered foods and will, therefore, decrease their consumption of all like products unless they can distinguish the one from the other. As noted above, FDA has invited further public comment on the labeling of food products developed through genetic engineering. In addition, in May 1993, FDA convened a joint meeting of two advisory panels to consider whether and how dairy products derived from cows treated with BST should be labeled as such.

FDA's policy has prompted legislative action. On June 16, 1992, a bill (H.R. 5401) was introduced to require the labeling of genetically modified food. In addition, in November 1992, the New York City Council voted to ask FDA to require the labeling of all genetically engineered food. Great Britain is also considering whether to require the labeling of foods developed through genetic engineering, according to CFSAN's Biotechnology Strategic Manager. The Codex Alimentarius Commission is likewise exploring the possibility of labeling foods derived from biotechnology in order to identify them for consumers who might not wish to buy or eat them.

Critics of mandatory labeling argue that requiring all genetically engineered food to be labeled would

- be expensive, if not impractical, because the complex components of a processed food product that had been developed through genetic engineering would be difficult to identify, track, and label;
- be difficult to enforce because analytical tests cannot detect whether a food substance has been genetically engineered; and
- imply a level of risk that is unsupported scientifically and might unduly alarm consumers and jeopardize consumers' acceptance of this technology.

Striking Proper Regulatory Balance Critical

The debate over FDA's policy and alternative regulatory approaches reflects a struggle between advocates of restraining government regulation and of giving government the authority to oversee industry. Striking the proper balance is critical for ensuring (1) food safety, (2) consumers' confidence in and acceptance of this new technology, (3) businesses' investment in and development of new products, and (4) ultimately, the success of a new industry important to the future competitiveness of the United States in a global economy.

According to CFSAN's Director, consumer acceptance is the key to realizing the potential of new biotechnology, just as it is of food irradiation. Food irradiation has had very limited application in the United States in large measure because food processors are concerned about negative public perceptions of its use. Consequently, U.S. consumers have experienced few benefits of this technology. Similarly, if consumers do not accept new biotechnology, they may forgo potential benefits, including improvements in nutrition, safety, availability, variety, affordability, and taste. In addition, consumers' reluctance to accept new biotechnology could jeopardize the nation's current commercial lead and future economic growth in this area.

Consumer and environmental groups and others believe that FDA's premarket approval of food developed through new biotechnology is necessary not only to evaluate the safety of new products but also to assure already skeptical consumers that genetically engineered food is safe to eat. Critics point out that if consumers do not have confidence in the government's and industry's assurances of safety—of which they are already distrustful—they will not accept genetically engineered food. Industry representatives acknowledge that FDA's backing will be essential to gain consumers' acceptance of their genetically engineered food products. However, they are concerned that extensive and costly premarket approval is not only unjustified scientifically but also unsound economically because it could put American industry at a competitive disadvantage if other countries did not impose similar requirements.

Part of the conflict over the regulation of new biotechnology concerns the basis for accepting genetically engineered food products. Industry and FDA scientists, among others, believe that the safety and acceptability of genetically engineered food should be determined by a scientific assessment of the risks posed by new products and their uses. These sources believe that a science-based approach to safety and regulation will provide the proper regulatory balance and use of limited resources. However, consumer and environmental groups and others believe that these safety assessments are at best uncertain because of (1) limitations in existing scientific methods, (2) limitations in society's experience with this new technology, and (3) the inability of science to prevent technological mistakes in the past.

Some critics believe that factors other than the scientific assessment of risk should enter into the evaluation and regulation of genetically engineered food. According to these critics, the federal government should consider the potential socioeconomic consequences (e.g., social, ethical, and economic) of genetically engineered food as well as the safety, quality, and efficacy of such products. Some have questioned the social utility of certain genetically engineered foods nearing commercialization because these foods are designed to improve production and processing and thereby reduce manufacturing costs but not to provide any direct benefit to consumers or the environment. For example, part of the controversy surrounding FDA's review of BST has been the perception that its use will

place family farmers at an economic disadvantage.[18] For others, human modification or manipulation of living organisms beyond the bounds of traditional breeding is morally wrong.

Others believe that the marketplace affords a more efficient and appropriate means than government regulation for determining the social utility of new biotechnology. In the past, the Congress has resisted imposing requirements for economic and social benefit as conditions for approving food additives. Currently, under FFDCA, FDA may not consider economic issues in deciding whether to allow the marketing of genetically engineered food.

Pressure to resolve the debate over the proper way to regulate new biotechnology is growing as some genetically engineered food products near commercialization and as interest mounts in promoting the nation's competitiveness in a global economy. However, this resolution does not appear to be imminent. First, FDA is still responding to the comments it has received on its biotechnology policy, and some aspects of this policy, such as labeling requirements, are evolving. Second, much of FDA's guidance to industry amounts to a case-by-case assessment of new products. Such an approach may produce regulatory uncertainty and inefficiency. Third, interagency coordination and jurisdictional issues remain to be resolved. FDA may need to sign memorandums of understanding with USDA and EPA to designate responsibility for regulating certain aspects of food and food ingredients developed through new biotechnology that cut across these agencies' jurisdictions. According to several industry, consumer, and environmental sources, regulatory uncertainty over genetically engineered food may hinder innovation, slow the commercialization of new products, and further undermine consumers' confidence in FDA's ability to ensure the safety of genetically engineered food products.

[18]A 1991 OTA report disputed this perception, concluding that use of BST would not alone economically disadvantage traditional farm operations but would, along with other factors, accelerate the preexisting trend—the pressure on traditional farms to grow or go out of business. U.S. Congress, Office of Technology Assessment, U.S. Dairy Industry at a Crossroad: Biotechnology and Policy Choices—Special Report, OTA-F-470 (Washington, D.C.: May 1991).

Novel Macro Ingredients

This appendix describes FDA's regulation of "novel macro ingredients" and covers (1) a definition of this new food technology, (2) examples of the products or applications of the technology, (3) possible food safety concerns, (4) FDA's responses to the technology, and (5) any unresolved regulatory issues. See appendix VI for information on FDA's responses to new food technologies and on unresolved issues that cut across specific technologies.

Definition

Novel macro ingredients are substances intentionally added to food products in relatively large quantities to modify the dietary intake of energy (calories) or to serve as a substitute for or to replace major dietary components, such as fats and sugars. Similar to "novel foods," as defined in the United Kingdom, they are

> foods or food ingredients produced from raw material, which has not hitherto been used for human consumption or which has been consumed in only small amounts, or produced by new or extensively modified processes not previously used in the production of food. . . . components extracted from conventional foods by traditional processes, recipe changes or minor process modifications are not considered to be novel foods.[1]

Applications and Examples

Novel macro ingredients are typically large quantities of digestible, partially digestible, or nondigestible substances with widely different chemical structures, physical properties, and biological effects. In contrast to typical food additives, which are used in amounts below 1 percent by weight of the overall food product, novel macro ingredients may be present in some foods in much greater amounts—above 10 percent by weight of the overall food product.

Industry is developing these products in response to emerging scientific information about the relationship of diet to disease and consumers' resultant concerns about the health effects of a diet high in fat and sugar and low in fiber. Novel macro ingredients have the potential to provide attractive food choices that may be beneficial in reducing weight and managing diet. They may allow manufacturers to modify traditional foods so that consumers can conform more closely to today's dietary recommendations without changing their eating behavior or preferences. According to one estimate, novel macro ingredients could become a

[1]James H. Maryanski, Ph.D., "Special Challenges of Novel Foods (Biotechnology)", Food Drug Cosmetic Law Journal, Vol. 45, No. 5 (Sept. 1990), p. 546.

trillion-dollar market and displace up to 20 percent of the market for dietary fat products.

According to FDA scientists, novel macro ingredients include a broad spectrum of substances that may be derived from traditional food sources, produced through chemical synthesis, or developed from novel sources. The following are examples of novel macro ingredients:

- A chemical compound known as sucrose polyester does not provide calories when eaten because it is not absorbed by the body. This effect is achieved at the molecular level through a subtle alteration that prevents the molecule from being processed as a food by the body. The substance is expected to replace the fat content of processed snack foods, such as potato chips, providing the texture and taste of fat without the calories.
- Egg and/or dairy protein molecules are specially processed with sugars and food gums through a method known as microparticulation. In effect, microparticulation creates food particles in a new shape that provides the texture of fat but is digested as a protein. This low-calorie fat substitute has been used in several frozen desserts in the United States.
- Natural substances, such as dietary fiber and gums, are used in proportionally large quantities. Interest in dietary fiber emerged in the mid-1970s, when scientists called for increasing fiber in the diet to help alleviate the risk of heart disease and cancer and to reduce caloric content. Industry responded to this call by introducing new products featuring fiber content—over 200 new products from 1988 to 1990, many of them containing oat bran. Certain food gums are also used to provide appropriate texture in fat-reduced foods.

Food Safety Concerns

Novel macro ingredients raise questions about the effects on human health and nutrition of displacing traditional dietary components. This displacement may occur through either the increased consumption of substitutes for traditional dietary components or the decreased consumption of traditional components. Some scientists are concerned that the consumption of novel macro ingredients could cause adverse nutritional effects, such as severe vitamin depletion, or adverse effects on bodily processes. For example, consumption of large quantities of partially or totally nondigestible substances could produce an undesirable laxative effect. Because the long-term effects of consuming some novel macro ingredients are uncertain and may take time to develop, some FDA scientists and others believe that postmarket surveillance of the rate and effects of consuming these ingredients will be necessary.

Uncertainty about how to test the safety of novel macro ingredients compounds uncertainty about their effects. There is no precedent or experience for evaluating the effects of the extensive changes in the human diet that these products are expected to produce. According to FDA and other scientists, the traditional studies of laboratory animals used to assess the safety of food additives may be inadequate to assess the safety of novel macro ingredients because these ingredients may be chemically more complex than traditional food additives and will comprise a far greater proportion of the human diet. They cannot be tested in animals at the high concentrations that could demonstrate a margin of safety above their projected level of use in the human diet. In standard tests for determining food safety, animals are fed quantities of a substance considerably in excess of the quantities to which humans would be exposed. Data on effects are then extrapolated to comparable human intake for a measure of safety. To assess the effects of displacing 10 to 15 percent of dietary fat through the use of a fat substitute, scientists would have to feed laboratory animals quantities of the substitute that the animals could not physically tolerate, according to CFSAN's former Associate Director of Clinical Nutrition. The animals would experience problems with their general nutritional status that would interfere with safety testing. Human clinical trials or other models may therefore be necessary to assess the safety of novel macro ingredients.

FDA's Responses

In general, depending on their nature and intended use, novel macro ingredients may be classified as GRAS substances or evaluated under FDA's regulation for direct food additives (see app. I). For example, FDA affirmed the GRAS status of the microparticulated egg/dairy protein product in 1990 for use in frozen desserts. FDA is currently evaluating the sucrose polyester fat substitute for use in snack foods under the direct food additive petition process.

FDA officials are aware of the safety concerns posed by novel macro ingredients and of the limitations of animal feeding studies for assessing the safety of these ingredients. In a paper detailing the agency's evolving regulatory perspective on these products,[2] FDA officials reported that the agency was reviewing novel macro ingredients case by case, using the petition for the sucrose polyester fat substitute as a basis for developing questions about the safety of these ingredients and approaches to regulation. In 1991, CFSAN took the first administrative steps required to

[2]J. E. Vanderveen, and W. H. Glinsmann, "Fat Substitutes: A Regulatory Perspective," Annual Review of Nutrition, Vol. 12 (1992), pp. 473-487.

develop and publish any regulations concerning the use of human clinical trials for testing novel macro ingredients. The process has not yet been completed. FDA has also drafted human clinical trial requirements and guidelines for CFSAN's guide to toxicological testing requirements.[3]

Outside experts are contributing to FDA's assessment of the safety of novel macro ingredients. The International Life Sciences Institute, an industry-funded, nonprofit scientific organization, has independently studied safety assessment questions for novel macro ingredients.[4] An FDA scientist sat in on the Institute's deliberations, acting as a resource and providing insight on the agency's views on various topics of concerns. According to this scientist, FDA has already identified many of the issues and safety questions that the Institute considered. FDA is also considering the use of an outside committee of food safety experts to identify safety questions and considerations for novel macro ingredients. FDA may convene a committee within fiscal year 1993, according to the Director, Office of Pre-Market Approval.

Unresolved Regulatory Issues

The proposed use of novel macro ingredients has raised several unresolved regulatory issues, including the need for human studies, the need for mandatory postmarket surveillance, and the appropriateness of allowing manufacturers to determine GRAS status. In addition, the uncertainty associated with regulating these products illustrates the difficulties of applying the existing regulatory framework for food and food ingredients to the products of new food technologies.

Need for Human Studies

Although scientists believe that human clinical studies may be needed to assess the safety of novel macro ingredients and, perhaps, of other novel food substances, such studies may be controversial. Section 409(i) of FFDCA gives FDA the authority to develop regulations to allow human investigational testing of unapproved food additives. However, FDA has not developed a policy or regulation on the use of human clinical trials or determined whether they should be mandatory for novel macro ingredient or other food additive petitions.

[3]FDA's safety data requirements are contained in Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Foods (also called the Red Book).

[4]Joseph F. Borzelleca, "Macronutrient Substitutes: Safety Evaluation," Regulatory Toxicology and Pharmacology, Vol. 16 (1992), pp. 253-264.

In addition, some scientists believe that the use of human clinical studies for food additives raises ethical questions because, unlike a drug, a specific food substance may not produce a direct health benefit to a consumer. The benefit of a food substance may be derived only in the context of a total diet. Furthermore, FFDCA does not permit FDA to weigh potential benefits against potential risks when reviewing new food additives. As a result, some scientists believe, human testing of novel, unapproved food additives may not be easy to justify. However, others believe that FDA should be permitted to weigh the benefits and risks of certain food additives, such as novel macro ingredients, that may provide some health benefit to consumers.

Need for Mandatory Postmarket Surveillance

FDA officials and others believe that mandatory postmarket surveillance may be necessary to identify potential, particularly long-term, health problems associated with the general public's—and with sensitive subpopulations'—consumption of certain new food substances, such as the products of new biotechnology or novel macro ingredients. According to the Director, Office of Pre-Market Approval, CFSAN, FDA may try to negotiate requirements for firms to conduct postmarket surveillance, including the collection and reporting of data on dietary use and on any adverse effects, as a condition for approving novel macro ingredients as food additives. In at least one instance, FDA has been able to obtain voluntary postmarket surveillance for a food additive (Aspartame, an artificial sweetener) as part of the approval process for this substance. However, FDA does not have the statutory authority to require surveillance for food products, as it does for human drugs, according to the Director. In addition, although FDA and other scientists have called for mandatory postmarket surveillance for all novel macro ingredients, GRAS or non-GRAS, FDA may not be able to negotiate such a requirement for GRAS substances.

FDA officials have also discussed restricted marketing as another means to evaluate the safety of novel food ingredients before exposing consumers generally. However, FDA does not have the authority to limit the entry into the market of food products, as it does of drugs, according to an FDA official.

Advisability of Continuing GRAS Self-Determination

FDA officials and others have expressed reservations about industry's ability to self-determine the GRAS status of a novel food ingredient or of the expanded use of a substance previously determined to be GRAS and to market the substance either without the agency's knowledge or while

pursuing FDA's affirmation of the ingredient's GRAS status. (See app. I for a discussion of the procedures for determining GRAS status and app. II for a discussion of FDA's options for responding to industry's self-determination of GRAS status.)

Others, however, believe that the GRAS provisions give FDA a flexible mechanism to rank-order expenditures of limited resources and to focus its efforts on food additives posing the greatest concern to public health. In addition, GRAS self-determination allows industry to introduce new products without pursuing the time-consuming and resource-intensive food additive and GRAS affirmation petition processes.[5] For example, in April 1992, Mars, Inc., began marketing a light version of its Milky Way bar that contained a reduced-calorie fat called "caprenin," manufactured from natural ingredients by the Procter and Gamble Company. Although Procter and Gamble has petitioned FDA to affirm its determination that the use of caprenin in candy is GRAS, the company was first able to self-determine the safety of this substance and begin marketing it for use in candy.

Effects of Regulatory Uncertainty

Our review of the food additive petition for Olestra—the noncaloric sucrose polyester fat substitute discussed throughout this appendix—illustrated some of the scientific and regulatory issues that face both industry and FDA in applying the existing regulatory framework for food and food ingredients to novel food substances.[6] Procter and Gamble, the developer of Olestra, first discussed its product with FDA officials in May 1971; as of June 1993, FDA had not approved the use of Olestra as a food additive but was waiting to receive the results of a study of Olestra's effects on pigs. Because FDA did not have a process for approving food products, such as Olestra, that made health claims, Procter and Gamble initially pursued approval of the substance as a drug. After FDA relaxed its policy and began to permit health claims on food in the mid-1980s, Procter and Gamble filed a petition with FDA for approval of Olestra as a food additive. Although several factors contributed to the extended regulatory review of Olestra, this example clearly shows that unique products may

[5]Frederick H. Degnan, "Rethinking the Applicability and Usefulness of the GRAS Concept," Food, Drug, Cosmetic Law Journal, Vol. 46 (1991), pp. 553-582.

[6]FDA Premarket Approval: Process of Approving Olestra as a Food Additive (GAO/HRD-92-86, Apr. 7, 1992).

take considerable time to review and approve—in this instance, well over 20 years.[7]

FDA's approach to regulating novel macro ingredients is evolving as the agency evaluates new types of food safety data generated for the food additive petition for Olestra. However, industry officials and others have voiced concerns about the chilling effect of regulatory uncertainty on product innovation and development. According to some industry officials, FDA does not have a consistent approach for requesting safety data and making safety determinations. In addition, industry and academic scientists said, FDA's food additive petition processes are too slow and may therefore also inhibit the development of new products. According to several industry officials, FDA needs a regulatory system for emerging technologies.

FDA officials contend that the agency tries to provide general guidance on scientific concerns and methods for working with the agency until a specific product is ready for review by staff. In their view, it is not the agency's job to tell industry how to guarantee safety. Consumer advocates have also expressed the opinion that FDA should be concerned with regulation and the enforcement of product safety, not with economic development.

According to the Subcommittee on Foods, Cosmetics, and Veterinary Medicine, Advisory Committee on the Food and Drug Administration[8] —an independent blue ribbon panel created by the former Secretary of the Department of Health and Human Services, FDA's parent organization—FDA is viewed as slow in approving products and writing regulations. The Subcommittee concluded that FDA must recognize that approving useful and safe new products can contribute as much to public health as preventing the marketing of harmful or ineffective products. The Subcommittee recommended a number of steps to avoid delays, including

- developing a streamlined process for reviewing and approving documents;
- using expert advisory panels to assist in reviewing products; and
- establishing priorities and criteria for reviewing different products, such as direct and indirect food additives.

[7]Although several bills were introduced into the 102nd Congress to extend the terms of Olestra's patents to compensate for the extended regulatory review of this substance, the session ended before the bills were enacted.

[8]Final Report of the Advisory Committee on the Food and Drug Administration (Washington, D.C.: May 1991). The Committee was commonly known as the Edwards Committee, after Charles C. Edwards, M.D., Chairman.

In 1992, we recommended that the Commissioner, FDA, develop a single automated tracking system to improve the management by the agency of its regulation process.[9]

FDA officials explained that delay sometimes occurs because traditional safety tests cannot be used to evaluate novel food substances and, therefore, new tests and approaches must be developed and validated to assess safety—both of which take time. In addition, some FDA officials said that delays occur, in part, because the existing statutory provisions are complex and, in some cases, are inconsistent and scientifically outdated. They noted that the existing food additive provisions do not distinguish between categories of additives with substantially different impacts on public health. (See app. V for information on FDA's recent proposal to establish a threshold of regulation for indirect food additives.) Some industry officials and others have proposed that FDA establish a fast track for processing petitions for food additives that provide some positive public health benefit to encourage manufacturers to develop beneficial new products. However, FDA has not proposed such a system, in part because of the difficulty in defining the criteria for priority, according to the Director, Office of Pre-Market Approval.

[9]FDA Regulations: Sustained Management Attention Needed to Improve Timely Issuance (GAO/HRD-92-35, Feb. 21, 1992).

Functional Foods

This appendix describes FDA's regulation of functional foods and covers (1) a definition of this new food technology, (2) examples of the products or applications of the technology, (3) possible food safety concerns, (4) FDA's responses to the technology, and (5) any unresolved regulatory issues. See appendix VI for information on FDA's responses to new food technologies and on unresolved issues that cut across specific technologies.

Definition

Manufacturers and others are researching and developing new food products to enhance human health and lower the risk or inhibit the onset of certain diseases, such as cancer. Although there is no generally accepted term for these products, they are variously referred to as "functional" foods, "tailored nutrition" foods, "pharm" or "designer" foods, "nutritionally engineered" foods, or "nutraceuticals." Generally, these products are formulated with naturally occurring chemicals (or combinations of chemicals)—found in many fruits, vegetables, grains, herbs, and spices—to provide a health benefit, lower the risk of certain diseases, or affect a particular body process. They go beyond correcting diseases, such as pellagra and scurvy, caused by nutritional deficiencies.[1]

Functional foods are akin to novel macro ingredients (see app. III) in that their formulation is intended to provide a health benefit to consumers. However, functional foods are designed to lower the risk of specific diseases, such as lung cancer, by removing certain ingredients, by adding or combining ingredients not normally found in a food product, or by concentrating substances in higher-than-usual quantities. Novel macro ingredients are food additives designed to replace or reduce major dietary components, such as fats and sugars, and to provide a general, more indirect health benefit, such as a decreased risk of heart disease.

Applications and Examples

Functional foods are a developmental outgrowth of recent scientific research on the relationships between diet and health and the demands of increasingly health-conscious consumers. Advocates have argued that these new products will help to reduce the nation's skyrocketing health care costs by promoting health, inhibiting disease, and increasing longevity. For example, because as many as one-third of all cancer deaths

[1]The terms "functional food" and "nutraceuticals" do not encompass "medical foods"—products specially formulated for persons with specific medical disorders, diseases, or conditions, such as diabetes, kidney disease, or recovery from surgery. Medical foods must be used under a physician's supervision, and they are designed to provide calories (energy) or specific nutrients required because of the medical condition.

may be related to diet, advocates believe that functional foods will help to inhibit the onset of some of the forms of cancer that, taken together, rank as the second leading cause of death in the United States behind heart disease. According to FDA, more than 475,000 deaths were due to cancer in 1987, and the overall economic cost of the disease was estimated to be $72.5 billion. Some advocates of functional foods have suggested that the very foods that once contributed to illness and disease may eventually be reconstructed to offer significant health benefits. In the future, for example, cocktails, candy, ice cream, and hot dogs may be designed to fight cancer.

Functional food products could take many forms, ranging from isolated nutrients and dietary supplements (e.g., vitamins, minerals, herbs) to genetically engineered foods, herbal products, and processed products, such as cereals, soups, and beverages. In concept, however, they are intended to go beyond foods fortified with vitamins or minerals and may contain specific food components that scientists have determined can mitigate or alleviate a disease or health-related condition, according to the Director, CFSAN.

The National Cancer Institute has a 5-year, $20.5 million program to study the inhibitory effects of specific plant chemicals on cancer. For example, the Institute is studying sulfur compounds found in garlic and onions that may inhibit stomach cancer and beta carotene, a yellow-orange pigment found in carrots and in other green/yellow vegetables and fruit, that may inhibit lung cancer. The Institute also plans to study chemicals in flax seed, citrus fruit, and licorice root. The goal of the program is to develop processed foods that are supplemented with food ingredients naturally rich in cancer-inhibiting substances and that are also stable, safe, and palatable.

Safety Concerns

FDA officials and others are concerned that increasing the concentration or consumption of certain chemicals in foods, even of naturally occurring chemicals, to anticarcinogenic levels could prove toxic to humans. For example, large amounts of vitamin A can cause illness and even death. In addition, increasing the consumption of a certain nutrient could decrease the consumption of other nutrients and food substances that also reduce the risk of certain diseases.

Some food scientists and nutritionists are concerned that the use of functional foods may impede efforts to convince Americans to eat a

healthier diet because some consumers may prefer to rely on a "magic pill" than to modify their diet. Some scientists are also concerned that functional foods may encourage some people not only to continue eating less healthy foods but even perhaps to eat more of them on the assumption that they are somehow protected. Furthermore, concern has arisen that the allure of functional foods may cause dramatic shifts in the American diet before enough time has elapsed to assess the long-term safety of these products. For example, extracting the components of vegetables and placing them in another food form does not guarantee the creation of the new food form that will produce the same effects as a high-vegetable diet, according to an FDA official.

FDA's Responses

FDA has responded to functional foods both by applying existing statutorily imposed requirements and by conducting research.

Because there is no regulatory category for functional foods, FDA could regulate these products as foods, drugs, or both, depending on their intended use and form. If classified as a food, a functional food could be regulated as a whole food, a food additive, or a GRAS substance (see app. I). In addition, a functional food could be regulated as a "special dietary use food." Any health benefit claims for the product would be regulated under the provisions of the Nutrition Labeling and Education Act of 1990 (NLEA).

Under section 411 of FFDCA and FDA regulations, special dietary use foods are distinguished from general foods because they

- supply particular dietary needs that arise from physical, physiological, pathological, or other conditions, such as food allergies or obesity;
- supply particular dietary needs that are related to age; and
- supplement or fortify food with any vitamin, mineral, or other dietary substance (i.e., dietary supplements).

Commonly called the Proxmire Amendment after its sponsor, section 411 was enacted in 1976 in response to concerns about the overregulation of dietary supplements. The amendment restricts FDA's ability to establish maximum limits on the potency of any vitamin or mineral dietary supplement unless safety is a concern. The amendment also prevents FDA from classifying a dietary supplement as a drug because the level of a vitamin or mineral in the supplement is higher than the agency considers to be nutritionally rational or useful. However, FDA may regulate a product as a drug if it contains a dietary substance at levels that are intended to be

therapeutic and are therefore far above the level that is normally characteristic of food. According to FDA, the agency would consider the appropriate upper limit on any substance case by case. Generally, vitamin and mineral supplements are considered foods, not drugs, unless the label claims that the product is therapeutic.

FDA will regulate functional food claims under the provisions of NLEA. Among other things, this act authorized, for the first time, for both conventional food and dietary supplements, the use of health claims that characterize the relationship of a food substance to a risk of disease or a health-related condition. Before NLEA was enacted, products that made health or disease claims were classified as drugs.

Under NLEA, a health claim may be made for food substances only when FDA provides for the claim by regulation. In general, FDA may permit health claims for food substances when qualified scientists agree that publicly available evidence links a food substance with a reduction in the risk of a disease or health-related condition common to the general population. For example, the label for a product containing calcium may be allowed to state that adequate dietary intake of foods high in calcium may reduce the risk of osteoporosis.[2] NLEA required that FDA initially consider 10 topics associating substances with diseases and health-related conditions and issue regulations for establishing new disease prevention or health claims. FDA's final regulations implementing the NLEA provisions, published in January 1993 and effective in May 1993, allow claims for seven relationships between a nutrient or a food and the risk of a disease or health-related condition and lay out general requirements for future claims. FDA denied three diet/disease claims because the agency concluded that scientific evidence did not support the claims at this time. FDA is, however, reviewing additional evidence with respect to at least one of these claims.

If a functional food was claimed to cure, mitigate, treat, or prevent a disease or otherwise affect the structure or function of the body, then FDA would regulate it as a drug. According to FDA, a medical or therapeutic claim implies a degree of association between a substance and a disease that is not supportable for any food substance at this time.

[2]Osteoporosis, a disease that causes human bones to deteriorate, affects between 15 million and 20 million Americans, particularly elderly women, who comprise a growing percentage of the population. According to FDA, the disease is responsible, annually, for about 50,000 deaths and over $10 billion in health care costs.

The classification of a product is significant because drugs have to meet more stringent efficacy requirements than food additives as well as stricter regulations controlling their manufacture and marketing and reports concerning adverse health effects. For example, drug manufacturers must demonstrate to FDA, often with data from human clinical studies, that their products are safe and effective for the uses intended before the manufacturers may market them. The scientific standard for medical claims for drugs is also more stringent than that required for health claims for food. However, under FFDCA, drugs may be used if their benefits outweigh their risks, whereas food additives are evaluated on the basis of risk alone. Classifying functional foods as drugs could, then, permit the marketing of a product that had been shown to benefit persons with a particular disease or health condition even if that product was not totally risk-free.

FDA is also conducting research on functional foods—specifically, on food anticarcinogens—under an interagency agreement with the National Cancer Institute. The work scheduled for the first 2 years of the agreement has been completed, and final research reports have been submitted to the Institute. The research is designed to evaluate the nutritional safety of specific food extracts that may be taken in increased doses to lower the risk of cancer.

Unresolved Regulatory Issue

Various commentators from industry, government, and consumer groups believe that advances in science and technology and changes in the food supply, especially the increasing association of certain food substances with disease prevention, will further blur, if not erase, the legal boundary line between foods and drugs. Some believe that this blurring will require a fundamental rethinking of the statutory classifications and applicable safety standards for foods and drugs. For example, some industry representatives we spoke with said that it may be time to consider a risk/benefit system for regulating certain food additives that provide specific health benefits. Furthermore, advocates of nutraceuticals, like advocates of dietary supplements, believe that these products cannot properly be classified as either foods or drugs. These critics believe that a new regulatory classification and review system must be developed for these new products. How functional food products would be classified and regulated could significantly affect the regulatory burden and associated costs for manufacturers and, ultimately, the availability of these products.

According to advocates of nutraceuticals, neither the food nor the drug classification provides manufacturers with a mechanism to recoup the costs of developing and marketing these products. A health claim for a food substance is not a license, and once a health claim has been established, it may be used by any company whose food substance meets the criteria for the claim. Furthermore, since the claim must be based on publicly available scientific data, the manufacturer must make proprietary data public in order to receive FDA's approval of the health claim. Because natural substances are not patentable, advocates of nutraceuticals claim that companies have little incentive to expend the resources necessary to pursue approval of their products as drugs because they cannot, through exclusive marketing, recover the costs incurred. They are also concerned that regulating these products as drugs would be too costly and time-consuming. Thus, these advocates claim, manufacturers are discouraged from investing in the research, development, and marketing of innovative products and uses—to the detriment of consumers' health.

A nonprofit trade association that advocates wider use of nutraceuticals has proposed the establishment of a new regulatory category for nutraceuticals under which proprietary or exclusive medical or health claims for nutraceuticals could be made on the basis of substantially fewer data requirements than are needed to establish a claim in a new drug. This association has urged the use of the Orphan Drug Act as a model for granting exclusive marketing rights. Under the Orphan Drug Act, exclusive claims can be based on the research and development sponsored by a company for 7 years after a product's approval—regardless of patent protection. Advocates of nutraceuticals maintain that both Europe and Japan are ahead of the United States in recognizing claims for nutraceuticals.

However, others believe that food nutrients used to inhibit the onset of specific disease should be subject to the same standards of safety, efficacy, and quality control as traditional drugs. FDA, for instance, believes that the historical marketing record of dietary supplements does not justify unique treatment. In FDA's view, the safety problems associated with L-tryptophan (see app. II) and the widespread health fraud associated with the labeling of some dietary supplements support stronger rather than more lenient regulation of these products.

The controversies over how to regulate the health claims of dietary supplements may be precursors of controversies over how to regulate the safety and health claims of functional foods. As the enactment of the

Proxmire Amendment in 1976 indicated, the regulation of dietary supplements has proved controversial. Within the last year, several bills have been introduced into the Congress to create a new statutory category for dietary supplements in response to long-standing complaints by industry representatives and others that these substances are neither drugs nor food additives but a unique type of food that should be regulated differently. Furthermore, in October 1992, the Congress responded to the concerns of vitamin manufacturers and others by imposing a moratorium until December 15, 1993, on the implementation of the 1990 NLEA amendments affecting health claims on dietary supplements in order to allow more time to study the regulation of these products.[3] Some segments of the dietary supplements industry had been concerned that FDA's approach would be unduly restrictive and tantamount to a ban on such products. Although NLEA allowed FDA to develop different standards for assessing health claims for dietary supplements than for conventional foods, FDA's regulations would have applied the same standard for all food substances. FDA recognized when it proposed the regulations that its approach was contrary to the view expressed by some Members of Congress and others that a separate, more lenient standard should be established for dietary supplements. During the moratorium, the Congress is expected to consider the results of studies from GAO and OTA that it mandated on the regulation and enforcement of dietary supplements. As part of this effort, the Congress may consider whether the existing statutory classification of dietary supplements as foods is appropriate, whether these products should be regulated as drugs, or whether a new statutory category and safety standard should be established.

[3]Dietary Supplement Act of 1992 (P.L. 102-571; Oct. 29, 1992).

New Food-Packaging Technologies

This appendix describes FDA's regulation of selected new food-packaging technologies and covers (1) a definition of these new technologies, (2) examples of the products or applications of the technologies, (3) possible food safety concerns, (4) FDA's responses to the technologies, and (5) any unresolved regulatory issues. See appendix VI for information on FDA's responses to new food technologies and on unresolved issues that cut across specific technologies.

Definitions

New packaging technologies are new techniques and materials used to package food products, either raw or precooked. Existing packaging technologies include canning, bottling, and freezing foods and using chemical preservatives in food and/or packaging materials to avoid the need for refrigeration. New packaging technologies are arising from industry's need to reduce costs and/or respond to consumers' demands for specific products.

Applications and Examples

The new technologies discussed in this appendix include packaging for a new generation of refrigerated foods, microwaveable packaging, and recyclable packaging.

New Generation Refrigerated Foods

These types of foods are often packaged by methods intended to increase their shelf life by reducing or eliminating the oxygen in contact with them. These foods require constant refrigeration, but packaging can extend their shelf life—the time a product can remain safe for sale—from 2 to 10 weeks. One example of a technology that combines processing and packaging is the "sous vide" technology. Foods are vacuum packed and then cooked, chilled, and stored under refrigeration. The product is then reheated before being consumed. (The term "sous vide" may also refer to the final end product.) Such processes do not induce the changes in flavor or texture caused by higher temperatures.

Another technology is modified atmosphere packaging, in which food is packaged in an atmosphere containing little or no oxygen. Packaging materials, such as various types of plastic, may also be used to create partial or complete barriers to oxygen molecules; to release or absorb gases, such as carbon dioxide; to reduce the oxygen content or allow further processing of the food within the container; and to release chemicals to extend shelf life or reduce the growth of mold. Such

packaging is used for fresh meats, prepared sandwiches, salads, fresh pasta, baked goods, and produce available in retail outlets. These products respond to consumers' demands for tasty, low-processed (e.g., few chemical preservatives) or fresh, and convenient foods at the retail level. Sales of vacuum packed foods in plastic containers are expected to grow from $250 million in 1988 to $700 million in 1993. Centrally prepared and packaged refrigerated foods are also used at restaurants to reduce the need for labor-intensive meal preparation and thereby lower overhead costs.

Microwaveable Packaging

These materials contain prepared foods that are to be heated or cooked in a microwave oven. Microwaveable containers can be used for frozen, fresh, and shelf-stable products. Materials used in microwaveable containers include plastics; composites of fiber, plastic, and/or metal; and adhesives used to bind two or more materials. Because heat is generated within the food, microwaved foods do not brown. Heat susceptor technology (i.e., molecules of metal embedded in packaging) was developed to raise temperatures and produce a browning effect. These microwave-absorbing "heat susceptors" (microwave susceptors) create high temperatures in excess of 450 or 500 degrees Fahrenheit and are frequently used for packaging microwave popcorn and pizza.

Microwaveable products include breakfast and dinner entrees, such as burritos, omelets, pizza, pasta and rice dishes, soup, and sandwiches; snacks, such as corn dogs and popcorn; and baked goods, such as brownies. These products are designed to be either heated or cooked in a microwave oven. Microwaveable products respond to consumers' demands for quick, convenient foods, many of which are packaged in single portions or for children.

Recyclable Packaging

Virgin materials are collected after consumer use and remanufactured (recycled) for reuse as food packaging. A number of materials used in packaging foods can be recycled, including glass, steel, aluminum, paper, and certain plastics. Packaging for food and beverages contributes an estimated 10 to 20 percent of total municipal solid waste, or about 390 billion pounds per year, according to FDA. According to a food industry publication,[1] consumers' demands have inspired the production of "green" packaging to address environmental concerns and have moved the food

[1]Prepared Foods: New Products Annual 1991 (Illinois: Gorman Publishing Company, 1991), p. 18.

industry toward source reduction[2] and recyclable materials. According to industry analysts, environmental issues are likely to remain a major factor in packaging, and firms addressing these concerns will gain a distinct marketing advantage. Furthermore, several states and the Congress have considered bills that would mandate the use of recyclable and recycled plastics for packaging, including packaging for food.

Food Safety Concerns

Food safety concerns associated with food packaging depend upon the type of packaging material, the technique for processing the food, and the way the consumer handles and uses the packaging. New generation refrigerated foods may become contaminated; microwave cooking may cause chemical compounds to move from the packaging to the food (called migration); and recycled materials used for food packaging may contain contaminants.

Potential for Disease

According to food scientists, modified atmosphere packaging retards the growth of microorganisms that cause evidence of food spoilage, such as discoloration or offensive odor. However, these technologies do not eliminate pathogenic (disease-causing) microorganisms. Products packaged in this manner must be kept under constant refrigeration because they contain few or no chemical preservatives. If a product is not kept under constant refrigeration, it may look and smell safe to eat but may contain pathogenic microorganisms. In addition, adequate refrigeration alone does not prevent the growth of some pathogenic microorganisms, such as Listeria monocytogenes, that can grow at refrigeration temperatures. Application of this technology may pose more of a concern at the retail than at the food-processing level because retail establishments usually have fewer quality controls than food processors or manufacturers. In addition, because these products may resemble familiar shelf-stable products, retailers and consumers may not recognize or understand the need for constant refrigeration.

Migration of Chemicals

FDA scientists discovered in 1987 that, when heated in microwave ovens under actual conditions of use, heat susceptor packaging often reached temperatures in excess of 450 or 500 degrees Fahrenheit. Such temperatures were much higher than the 300 degrees Fahrenheit envisioned as the maximum temperature to which food-packaging

[2]Source reduction is the design and manufacture of products and packaging with minimum toxic content, minimum volume of material, and/or a longer useful life.

materials would be exposed when many of these materials were originally approved. Because the rate at which packaging materials migrate into food increases rapidly with increases in temperature, the use of such packaging materials at temperatures above 300 degrees Fahrenheit could significantly raise levels of migration into food.

Introduction of Contaminants

Recycled materials that have not been thoroughly cleaned or containers that have been used to store hazardous materials could introduce contaminants, such as traces of carcinogenic chemicals, during remanufacturing. These contaminants could then eventually come in contact with food products when the remanufactured materials were used for food packaging. According to FDA officials and others, processes used to recycle some materials, such as plastics, may not remove these potentially harmful contaminants. For biodegradable packaging materials, as for any other indirect food additive, concern focuses on the extent of contact with food products and the safety of the materials. Biodegradable packaging material that contains a biological component, such as starch, could be attacked by microbes, allowing contamination of the food product within.

FDA's Responses

In general, FDA regulates new food-packaging technologies by applying the existing regulatory framework for food and food ingredients to the materials and food substances used in the packaging. Packaging materials may be classified as indirect food additives (unless they are GRAS or prior sanctioned substances), and they may be evaluated for safety through FDA's premarket food additive petition process. Recycled materials that come into contact with food may require FDA's approval; if they do not receive this approval, the foods packaged in them may be considered adulterated and subject to an FDA enforcement action. GRAS and prior sanctioned packaging materials are also subject to FDA's postmarket surveillance. For example, certain plastic films used to wrap food, which were sanctioned by the federal government before 1958 and are therefore exempt from premarket review as food additives, could become adulterated and subject to an FDA enforcement action. In addition, applications of new food packaging are subject to FDA's current good manufacturing practices regulations (see app. I). In particular, FDA regulations require that any substance used as a component of an article that comes in contact with food must be of suitable purity for its intended use.

Discussion of FDA's responses to specific new packaging technologies follow.

New Generation Refrigerated Foods

CFSAN, with assistance from FDA's National Center for Food Safety and Technology,[3] is conducting research on the growth of Clostridium botulinum (the bacterium that causes botulism, an acute food poisoning) in seafood marketed in modified atmosphere packaging. This research provided the technical basis for model guidelines that FDA developed for state agencies to use in regulating modified atmosphere packaging at the retail level. These guidelines are interpretations of FDA's model food codes and provide direction on the application of the codes for regulating modified atmosphere packaging.[4] The agency developed the guidelines in response to inquiries about the technology from state and local authorities. In addition, FDA officials have provided informal guidance on the subject through seminars and correspondence.

Microwave Packaging Materials/Microwave Susceptors

FDA does not have a formal policy for dealing with microwave packaging materials and the safety questions they raise. The agency has been gathering information and performing research to establish a basis for a regulatory policy on these issues.

In September 1988, FDA held a public meeting to discuss its concerns about microwaveable packaging, the results of preliminary tests of microwave susceptors, and the data requirements for evaluating the safety of packaging materials used at high temperatures. This meeting focused specifically on the problems posed by microwave susceptors, as opposed to all microwave packaging.

In 1989, FDA published an Advance Notice of Rulemaking for microwave susceptor packaging. FDA requested data from industry on the temperatures to which packaging materials may be subjected and the subsequent migration of substances at these temperatures. The agency announced its intention to establish maximum temperature levels for the indirect additives that currently do not have such limits. The Advance Notice of Rulemaking also contained proposed data requirements for an

[3]See app. VI for a description of the National Center.

[4]The model codes include The Food Service Sanitation Code (1976), The Vending of Food and Beverages (1978), and The Retail Food Store Code (1982). FDA develops and promotes adoption of these codes to assist state and local authorities in regulating food safety.

evaluation of high-temperature effects and requested general comments on the need for, and nature of, regulations for high-temperature limitations.

FDA officials have reviewed most of the data submitted by industry and have compiled some regulatory options for microwave susceptor packaging. According to an FDA official, a review of the data submitted by industry indicated that there were no short-term safety problems related to microwave susceptor packaging but the possible effects of long-term exposure to migrating chemicals were still under review. Furthermore, FDA has presented its regulatory options for microwave susceptor packaging in a decision memorandum prepared for the Commissioner. The options are currently being reviewed by divisions within CFSAN. CFSAN is also developing analytical methods to detect residues from microwave packaging materials and models for evaluating the safety of substances that migrate under exposure to high temperatures. The results of this research will be used to support any proposed regulation governing heat susceptor packaging. According to the Director of FDA's Novel Ingredient and Policy Development Branch, FDA's policy may require manufacturers of susceptor packaging to obtain FDA's approval before marketing susceptor packaging. In addition, FDA may amend the authorizing regulation for a primary component of microwave susceptor packaging to specify temperature limits within which the material can be used without additional FDA approval.

Recyclable Packaging

FDA supports efforts to recycle plastic materials that come into contact with food, as well as traditionally recycled materials, such as metal, paper, and glass. According to the Director, Office of Pre-Market Approval, CFSAN, FDA intends to regulate recyclable plastic packaging under its authority for regulating the safety of indirect food additives. However, the agency has not issued a rule to cover the individual cases presented to the agency. Instead, FDA currently reviews proposed uses of recyclable plastic packaging, such as the packaging for soda bottles, case by case. Agency staff review the data submitted by a company on its recycling and testing processes to compare the characteristics of the recycled to the virgin material and to evaluate the possible migration of substances into food. Staff determine whether the recycled material is "substantially identical" to the virgin material that has previously been approved for use. FDA communicates its decision on the suitability of the material for recycling as food packaging through correspondence to the company, not through a food additive regulation published in the Federal Register. These decisions are specific to each company's process and are not generally applicable, as

are food additive regulations. The agency has announced, however, that when the intended use of recycled materials is inconsistent with existing regulations, new food additive regulations may be required.

CFSAN formed a task group in 1991 to develop guidelines for evaluating and regulating the safety of ingredients used in recyclable packaging. The task group reviewed new ways to determine whether a recycled material was "substantially identical" to its nonrecycled predecessor, including testing methods, as well as the level at which the recycled substance could be detected. On the basis of the task force's recommendations, in May 1992, FDA developed informal guidance to assist manufacturers of food packaging in evaluating the suitability of processes for producing food packaging from post-consumer recycled plastic. In addition, FDA announced that it intends to publish an Advance Notice of Proposed Rulemaking to gather additional information on the recycling of plastics and to outline its concerns about the use for food packaging of post-consumer recycled material that has already come into contact with food. However, an FDA official told us that no time frame had been set for accomplishing this task.

FDA is also participating in research on recycled plastics at the National Center for Food Safety and Technology. According to FDA, this research is designed to explore the types and levels of contaminants that may be found in recycled plastics.

Unresolved Regulatory Issues

Several issues associated with FDA's regulation of new food-packaging technologies remain unresolved, including the extent of FDA's authority to regulate new food technologies introduced at the retail level, the desirability of establishing a threshold of concentration for FDA's regulation of migrating substances contained in food packaging, and the impact of FDA's regulation on product development.

Extent of FDA's Retail Authority

Limitations in FDA's authority could impair the agency's ability to oversee new food technologies introduced at the retail level, especially if FDA does not provide timely guidance to state regulators. Although FDA has authority to ensure that a food product is not adulterated (i.e., injurious to health), its authority does not extend to the retail level unless the product is shipped or received in interstate commerce. In previous reports, we have concluded that FDA's need to verify that food establishments are involved in interstate commerce hinders FDA's oversight and is inconsistent with the

enforcement authority provided to USDA.[5] As a result, FDA generally relies on the states to regulate any safety concerns at the retail level, providing them with technical support and legislative guidance.

New food technologies at the retail level fall into a "gray" area of regulation. Some state officials have indicated that until FDA issues guidelines and a model ordinance on a food safety issue, their states will issue interim guidelines for dealing with a problem. For example, Illinois and Florida officials expressed concern about the safety hazards of modified atmosphere packaging and are responding to this new technology in the absence of guidance from FDA. In addition, one major food retailer noted that modified atmosphere packaging technology has increased the capacity for packaged food in retail stores. This company relies on regulatory agencies to approve and sanction new food technologies.

In general, FDA does not have the authority to require premarket approval for new packaging processes. Technologies such as modified atmosphere packaging may be developed and marketed without FDA's evaluation or approval. Although these processes must comply with FDA's current good manufacturing practices regulations, FDA's authority to regulate the products of these technologies may not be invoked until such time as the process/product can be shown to have adulterated the food or posed a safety hazard. As a result, FDA needs to provide timely guidance to the states to ensure the safety of new food technologies introduced at the retail level.

Desirability of Establishing a Threshold of Regulation

To save time and resources, FDA plans to establish a threshold of concentration below which it would not regulate as food additives migrating substances contained in food packaging that did not have an effect on food safety. Although economical, such a threshold of regulation may prove controversial because some consumer advocates and others may consider it an attempt to deregulate certain substances that are sometimes found in packaging materials.

All substances that migrate or may be expected to migrate into food from food-contact materials, such as packaging materials, are subject to the premarket approval requirements for indirect food additives. However, in

[5]See Food Safety and Quality: Uniform, Risk-based Inspection System Needed to Ensure Safe Food Supply (GAO/RCED-92-152, June 26, 1992) and Legislative Changes and Administrative Improvements Should Be Considered for FDA to Better Protect the Public From Adulterated Food Products (GAO/HRD-84-61, Sept. 26, 1984).

some cases, the type and amount of migrating material have no significant effect on food safety. Therefore, FDA plans to establish a process for determining when the migration of a substance used in a food-contact article is so unlikely or so minimal as not to require the regulation of the substance as a food additive. Under this process, manufacturers would submit information to FDA on the proposed use of the substance; this information would then receive abbreviated review by FDA—in contrast to the time- and resource-intensive review typically required for food additive regulations. The information would be used to estimate the concentration of a substance in the diet—in this case, the amount of a substance used in packaging materials that might become part of a food product. FDA has determined that the dietary concentration level of regulatory concern, or the "threshold of regulation" for food-contact materials, would be 0.5 parts per billion (ppb). If the estimated dietary concentration of a substance was at or below 0.5 ppb, then the substance would be exempt from regulation as an indirect food additive. Known carcinogens would be excluded from consideration under this process because the Delaney Clause prohibits the use of carcinogens as food additives (see app. I).

Among other advantages, a policy establishing a threshold of regulation would, in FDA's view, allow the agency to better allocate its limited resources to review food additive petitions for substances that pose greater public health concerns. According to the Director, Office of Pre-Market Approval, 40 percent of CFSAN's food additive review resources are devoted to indirect food additive petitions for packaging materials. He estimated that about 10 percent of these petitions would be unnecessary under a threshold of regulation, freeing resources for reviews of direct food additives. Industry would also benefit because the establishment of a threshold of regulation would expedite the review and authorization of a food additive petition. FDA's proposed use of a threshold of regulation for indirect food additives would have a direct bearing on the regulation of microwaveable and recyclable packaging.

FDA's proposal is an attempt to deal with statutory categories of food substances that are based on use or route of entry into the food supply rather than on risks to human health. In 1979, the National Academy of Sciences concluded, in part, that the existing categories inhibit the allocation of regulatory measures and resources in proportion to the degree of risk presented by various food substances. As explained in appendix II, the Academy recommended that the Congress replace the existing categories with a single risk standard applicable to all food substances.

Impact of Regulation on Innovation

While FDA's foremost mission with respect to food is to promote and protect the public health by ensuring that the food supply is safe, nutritious, wholesome, and truthfully labeled, FDA recognizes its role to foster innovation in food and food products. However, delay in, and uncertainty concerning, regulatory review and approval can cloud consumers' perceptions of safety and create barriers to developing and introducing new food technologies and products into the market. Prompt regulatory review is important not only to protect public health but also to foster consumers' confidence in, and acceptance of, new products or technologies and to provide a level playing field for manufacturers.

Despite these objectives, industry officials and others have said that FDA has taken too long to develop policies on microwave susceptors and recyclable plastic packaging and that the agency's slow pace inhibits the development and marketing of new products. However, as FDA officials have noted, some of the issues involved are complex and require time-consuming scientific research to resolve. In addition, these activities must compete for resources with FDA's other food-related responsibilities. For example, FDA's efforts to meet the mandated time frames for implementing the Nutrition Labeling and Education Act of 1990 drew resources away from other activities, according to the Acting Senior Associate Director for Policy, Planning, and Strategic Initiatives.

Advances in food packaging, like other new food technologies, are likely to provide future regulatory challenges for industry and FDA. According to an FDA official, the microwave susceptor is by no means the only packaging material whose conditions of permitted use need to be reevaluated in response to advancing technology. For example, FDA is also concerned about the possible migration of potentially carcinogenic compounds from one type of plastic cling wrap that could be used on food during microwaving. Some of these materials were prior sanctioned food substances exempt from the food additive provisions.

As explained in appendix VI, FDA is developing a strategic plan for its food programs. This planning mechanism may help the agency to identify and expedite the resolution of safety and regulatory issues associated with new food technologies, including new packaging, thereby improving its ability to foster innovation.

Cross-Cutting Responses/Issues

This appendix discusses FDA's responses to new food technologies and to several unresolved issues that cut across specific technologies. In particular, the appendix examines efforts by FDA to plan for and conduct research on emerging food technologies and to revitalize its food programs. In addition, the appendix examines how limitations in FDA's enforcement authority and resources may affect the agency's ability to ensure the safety of products produced by new food technologies. Lastly, the appendix briefly discusses how operation in a global economy may affect FDA's regulation of new food technologies and products.

FDA's Planning Efforts

Although FDA had conducted several surveys of developments in food technologies, it had not, until recently, begun to develop a strategic plan to integrate, coordinate, and establish priorities for its many activities to respond to these technologies. FDA agrees that it is important to track the development of new technologies, and the agency made several efforts during the 1980s to determine the state and nature of technologies with a potential impact on the agency. In 1981, FDA completed a survey to identify emerging technologies likely to affect the agency and its work through 1996. In 1987, as noted in appendix II, CFSAN studied the food biotechnology industry to identify not only the companies developing genetically engineered food products but also the volume and types of products and processes that CFSAN staff might encounter. FDA had conducted a similar effort for the products of veterinary medicine derived from biotechnology in 1986. In 1988, CFSAN contracted for a study of emerging food safety and quality issues for the 1990s. Taken together, these studies show that the new food technologies discussed in this report are among the major technologies facing FDA.

FDA and CFSAN have been developing strategic plans for the agency and the food programs, respectively. In response to a request from the former secretary of Health and Human Services (HHS) for a strategic plan to establish goals, priorities, and approaches for the agency into the 21st century, FDA planners have compiled information on trends in FDA's operating environment, conducted a workshop with a futurist on the environment anticipated for FDA in 20 years (year 2012), and surveyed over 100 experts outside the agency to obtain their views on how the agency should set priorities. FDA officials have been revising a draft strategic plan in response to the anticipated influx of new resources from user fees for drug approvals (see the discussion of constraints on FDA's resources at the end of this app.) and the transition to a new administration.

CFSAN has also been developing a strategic plan for its food programs. As part of its reorganization, discussed below, CFSAN created a new Office of Policy, Planning and Strategic Initiatives that, among other things, is responsible for developing a strategic plan for the Center. CFSAN has, in part, been responding to both internal and external criticism that it lacked an integrated, coordinated strategy for managing its programs and setting priorities. Critics have maintained that without such a strategy, the Center was not well prepared to respond to new food technologies, such as biotechnology.

In the past, CFSAN has benefited from strategic planning—a management tool whose value in setting priorities is widely recognized. In 1982-83, CFSAN developed a comprehensive plan to chart its programs, missions, and goals for 5 years, from 1984 through 1988. According to FDA officials, this plan enabled CFSAN to implement several important initiatives, such as integrating research programs in toxicology and nutrition, addressing new concerns in food microbiology, and improving the Center's information management systems. In addition, CFSAN set program goals in its plan for responding to emerging food biotechnology, as well as to new processing technologies. Although CFSAN had planned to develop a new 5-year plan for the period from 1989 to 1994, the effort never occurred because of insufficient resources and management turnover, according to CFSAN's new Strategic Planning Strategic Manager. In the interim, CFSAN used an informal, incremental approach to identify and regulate the products of new food technologies and to develop new policy. The agency relied on its staff to review current research literature, attend conferences, and communicate with industry and academic counterparts to identify emerging technologies and safety issues. CFSAN did prepare annual technical plans, but these were mostly designed to manage and allocate resources to specific research projects rather than to provide long-term plans for the Center.

FDA's Research on Food Technologies

As an important part of its response to new food technologies, FDA has conducted and sponsored research on new technologies and their impact on the nutritional quality and safety of the nation's food supply. FDA believes that its scientists must keep pace with the constant changes and developments in food technologies in order to have the resident expertise and scientific base needed to evaluate the safety of new products and processes. In addition, because most food processors consider their formulations and processes proprietary information, they publish little of

their research in the scientific literature. Thus, FDA believes that its scientists must develop this expertise through laboratory research.

According to a recent report by an FDA contractor, FDA spent about $70 million on food science research in fiscal year 1991.[1] CFSAN has focused most of its efforts on developing methods to detect specific chemicals or microbes in food, such as pesticide residues. FDA is also assessing the effects of certain new food technologies, trying to determine, for example, whether harmful products are created in the course of hydrogenating fish and vegetable oil. In addition, FDA is conducting research on certain novel food ingredients and technologies, including novel macro ingredients, modified atmosphere packaging, new food-processing techniques, and genetic engineering. For example, as noted in appendix IV, FDA is working to develop analytical methods to assess the nutritional safety of functional foods.

Despite FDA's belief that scientific research is critical to ensuring the safety of new food technologies, the agency has had difficulty sustaining its budget requests for these activities beyond the departmental level because some HHS officials believe that FDA should not be doing research, according to the Director, Planning and Management Communications Staff, Office of Planning and Evaluation. As a result, in the late 1980s, FDA did not receive the kind of budgetary support that it believed was necessary for research. According to a 1990 FDA report,

> The rate of technological advances in processing and packaging, as well as development of new packaging materials and new uses for traditional materials, has eclipsed FDA's research on safety and quality of the end products. As a result, many of these products enter the marketplace without thorough evaluation of the effect of processing or packaging on the safety or quality of the food. One recent example of this is microwave susceptor packaging and other high temperature uses of plastics.[2]

To revitalize CFSAN's food science research and help keep the Center abreast of technological changes, especially in the area of food processing and related food safety concerns, FDA, in 1988, created the National Center for Food Safety and Technology (National Center). The National Center, located outside Chicago, Illinois, is a research consortium among government, academia, and industry. Participants include FDA, the Illinois

[1]This figure includes research funding amounts for CFSAN, the Office of Regulatory Affairs, and the National Center for Toxicological Research, including salary and related personnel costs, operating costs, and central services costs. See GLH, Inc., Final Report: Foods Management Study, Contract No. 223-92-8053 (Falls Church, Va.: Oct. 16, 1992), p. 26.

[2]Food and Drug Administration, Comprehensive Needs Assessment 1994-1997 (1990), p. B34.

Institute of Technology, the Illinois Institute of Technology Research Institute, the University of Illinois at Urbana-Champaign Food Science Department, and 48 food firms. Since creating the National Center, FDA has awarded it contracts totaling $7.7 million. Contributions from industry and fees from members have provided additional funding. Funds from the state of Illinois's Department of Commerce, which were originally earmarked for the National Center, were not awarded in 1992-93 because of constraints on the state budget. The building facilities, which were donated by a major food processing company, were dedicated in May 1991.

The mission of the National Center is to study the effects of existing and new processing and packaging technologies, as well as of biotechnology, on food safety and quality. The National Center funds 12 positions; an additional 25 positions are funded directly by FDA. Current research projects focus on the safety of recycled plastics for food packaging, biotechnology, modified atmosphere packaging, and methods of automating and controlling food processing.

Although research at the National Center is still in the early stages, FDA has not formally evaluated the results of the consortium's efforts. In 1991, a blue ribbon panel created by the former Secretary, HHS, recommended that FDA pay close attention to, and continue to support, the developing research at the National Center. A year later, in an unofficial follow-up to their report, former members of the blue ribbon panel expressed the concern that

> there is no apparent advancement in the programs of the [National Center]. Although there are several ongoing projects with industry sponsorship, a number of these appear to be directed to food chemistry rather than the development and understanding of advanced food technology.

Efforts by FDA to Revitalize Its Food Programs

Over the years, our reports, as well as work by congressional committees, blue ribbon panels, and others, have criticized FDA's management and operation of the agency's food programs. For example, in 1991, the Advisory Committee on the Food and Drug Administration reported that

> There are deep concerns about the viability of the foods program and the lack of agency priority for food issues. Declines in resources and program initiatives during the past 10-15

years indicate a lack of agency management attention and interest in this area, although public interest in, and concern for, an effective food program remain high.[3]

Similarly, several individuals, including the Commissioner, FDA, have expressed concern that FDA's food programs have not kept pace with changes in food technologies and that the agency may not be prepared to handle emerging food safety issues.

In response, FDA has undertaken several efforts to revitalize and reshape its food programs and activities. FDA has (1) conducted a management study of CFSAN's programs and activities, (2) reorganized CFSAN and created organizational units to respond directly to certain new food technologies, and (3) established an advisory committee on issues related to food safety. These and other efforts, such as the announcement of a policy for reviewing new food plants developed by new biotechnology, may help FDA better respond to new food technologies, as well as better manage its existing food safety responsibilities.

Between November 1991 and October 1992, FDA and a contractor conducted a management and organizational study of the agency's foods programs, primarily those involving CFSAN. Among other things, the contractor surveyed FDA's food research efforts and scientific and regulatory policy issues relating to CFSAN. Working with FDA officials, the contractor also developed a new organizational structure for CFSAN.

In November 1992, FDA reorganized CFSAN into six program-based offices and several supporting offices. FDA believes that the new structure will increase managers' accountability for program results and streamline approvals. For example, FDA created an Office of Pre-Market Approval to consolidate personnel responsible for reviewing and approving food additives. In addition, to help prepare CFSAN for new food technologies and safety issues, FDA created an Office of Policy, Planning, and Strategic Initiatives. Senior staff members serving as strategic managers in this office will be responsible for cross-cutting policy, strategic initiatives, and scientific coordination in specific areas, such as biotechnology and microbiology. In effect, these managers will function in a capacity similar to CFSAN's Biotechnology Coordinator, the main focal point for all policy development and CFSAN representation on food biotechnology safety issues.

[3]Final Report of the Advisory Committee on the Food and Drug Administration (Washington, D.C., May 1991). The Committee was commonly known as the Edwards Committee, after Charles C. Edwards, M.D., Chairman.

This reorganization is significant because for almost 20 years CFSAN had been organized by scientific disciplines: toxicology, physical sciences, and nutrition. As might be expected, not everyone has been happy with CFSAN's reorganization. Some are concerned that the dispersion of scientific personnel among new program offices may threaten the Center's science base and impede consistency. However, FDA officials believe that the shift from an organization based on scientific disciplines to an organization based on programs will help integrate scientific disciplines with policy development, enabling the agency to respond more effectively to the needs of industry and consumers.

In addition to the general reorganization of CFSAN, FDA, in December 1990, created the Novel Ingredients and Policy Development Branch to identify and assess unique or unusual safety questions posed by novel food additive petitions and to develop policies for addressing these novel additives. Among other things, the Branch has been reviewing food additive petitions for novel macro ingredients, microwave susceptor packaging, and genetically altered enzymes, and it has been developing new policies, such as a proposal to establish a threshold of regulation for indirect food additives (see app. V).

In response to recommendations that it use more outside expertise to support its food science and regulatory activities, FDA chartered a Food Advisory Committee in December 1991 to advise the agency on emerging food safety, science, and nutrition issues. The 24 members of the Committee were drawn from academia, government, industry, and professional and consumer associations. At its first meeting in November 1992, the Committee considered

- the scientific capabilities and research that FDA needs to meet emerging food safety and nutrition challenges;
- human resource issues that face the agency, especially the ability to recruit and retain scientific personnel; and
- criteria for developing a risk-based food safety inspection system.

FDA also plans to establish a National Chemical Toxicants Advisory Committee in cooperation with USDA to provide advice on food safety issues associated with potentially toxic substances in food, including synthetic chemical contaminants, pesticide residues, and naturally derived chemical substances.

Despite the efforts that FDA has made to revitalize its food programs, several persistent cross-cutting issues may affect its ability to ensure the safety of new food technologies, including limitations in its enforcement authority and resources and the challenges imposed by a global economy. These issues may also affect the agency's ability to regulate new products produced by existing food technologies.

Limitations in FDA's Enforcement Authority

Existing limitations in FDA's authority to monitor food firms and take enforcement actions may affect the agency's ability to ensure the safety of new food technologies. We have previously reported on the limitations in FDA's enforcement authority, which we have contrasted with USDA's greater authority over meat and poultry products.[4] We have reported that FDA generally cannot

- presume that food firms are engaged in interstate commerce,
- require food firms to register with the agency,
- obtain access to manufacturers' production and distribution records,
- impose civil penalties for violations, or
- detain domestic products that violate food safety standards.

Two examples illustrate the effect of these limitations on FDA's ability to ensure the safety of new food technologies. First, except for firms that produce low-acid canned foods or infant formula, food producers and manufacturers are not required to register with FDA or even to inform the agency that they are in business. As a result, FDA is not aware of, and therefore does not oversee and inspect, some domestic food establishments. Because food products may enter interstate commerce without premarket approval from FDA, the agency may only learn about a new product after a problem has occurred—a point of particular concern raised by critics of FDA's policy towards genetically engineered foods (see app. II).

Second, lack of access to manufacturers' production and distribution records hinders FDA's oversight. According to FDA officials, access to a manufacturer's processing records is essential for ensuring the safety of

[4]See Food Safety and Quality: Uniform, Risk-based Inspection System Needed to Ensure Safe Food Supply (GAO/RCED-92-152, June 26, 1992); Legislative Changes and Administrative Improvements Should Be Considered for FDA to Better Protect the Public From Adulterated Food Products (GAO/HRD-84-61, Sept. 26, 1984); Pesticides: Adulterated Imported Foods Are Reaching U.S. Grocery Shelves (GAO/RCED-92-205, Sept. 24, 1992); Food Safety and Quality: FDA Strategy Needed to Address Animal Drug Residues in Milk (GAO/RCED-92-209, Aug. 5, 1992); Pesticides: Need to Enhance FDA's Ability to Protect the Public From Illegal Residues (GAO/RCED-87-7, Oct. 27, 1986); and Monitoring and Enforcing Food Safety—An Overview of Past Studies (GAO/RCED-83-153, Sept. 9, 1983).

final products, especially of genetically engineered products. Without this access, FDA inspectors cannot ensure that ingredients and processes are being used in approved and/or safe ways. For example, in at least one instance, an FDA field inspector was denied access to manufacturing documentation on a fermentation process that involved genetically altered organisms. The inspector believed that he needed access to these records to validate the firm's quality assurance procedures, testing of yeast cultures, and cleanup procedures.

Limitations on FDA's access to manufacturing records could also affect the agency's plans to adopt an inspection approach based on what is called a hazard analysis critical control points (HACCP). HACCP is designed to build quality into the manufacturing process at critical control points rather than to inspect it in product by product. Under a HACCP approach, FDA would monitor the manufacturing process by auditing industry records. FDA believes that a HACCP approach is essential for ensuring that manufacturing processes consistently produce safe products. The agency has been piloting such a system with seafood processors. However, restrictions on FDA's access to manufacturing records could hamper FDA's ability to require the implementation of such an approach.

Industry representatives told us that access to records should be voluntary, and they opposed efforts to expand FDA's authority on this point. These representatives expressed concern about FDA's using this authority unchecked. In addition, industry is concerned that FDA will be unable to protect proprietary data.

Attempts to expand FDA's enforcement authorities have been controversial in the past. Several bills were introduced in the last Congress to give FDA additional enforcement authority but were not enacted because of controversy over their scope, opposition from industry, and lack of support from the previous administration, which maintained that FDA had sufficient enforcement authority to protect public health.

Constraints on FDA's Resources

Current and former FDA officials and representatives of industry, consumer groups, and academia have maintained that a large disparity exists between FDA's food responsibilities and resources. According to many, FDA's resources are not only inadequate to meet the agency's current work load but will become further strained by the expected introduction of new products from emerging food technologies, such as new biotechnology.

Many have noted that FDA's facilities and equipment are deficient. The Advisory Committee on the Food and Drug Administration reported in May 1991 that many of the agency's facilities were overcrowded and poorly maintained and that scientific equipment was obsolete and inadequate to meet technological demands. For example, 32 percent of CFSAN's scientific equipment was due for replacement at the end of 1990. The Advisory Committee's Subcommittee on Foods, Cosmetics, and Veterinary Medicine went further, saying that "The present deplorable condition of FDA's food and veterinary medicine program facilities seriously jeopardizes the agency's ability to conduct credible regulatory activity." The Congress appropriated $200 million in fiscal year 1992 to begin improving FDA's facilities, and specifications for CFSAN's and CVM's laboratories are being developed.

Many have also expressed concern that FDA does not have enough staff and lacks expertise in specific scientific disciplines. Such limitations could affect the adequacy and timeliness of safety evaluations for existing and new products. For example, in an April 1991 speech, the Commissioner, FDA, estimated that the backlog of food additive petitions was growing at the rate of 10 to 15 petitions a year, adding to an existing load of 250. In the Commissioner's opinion, this backlog was unacceptable.

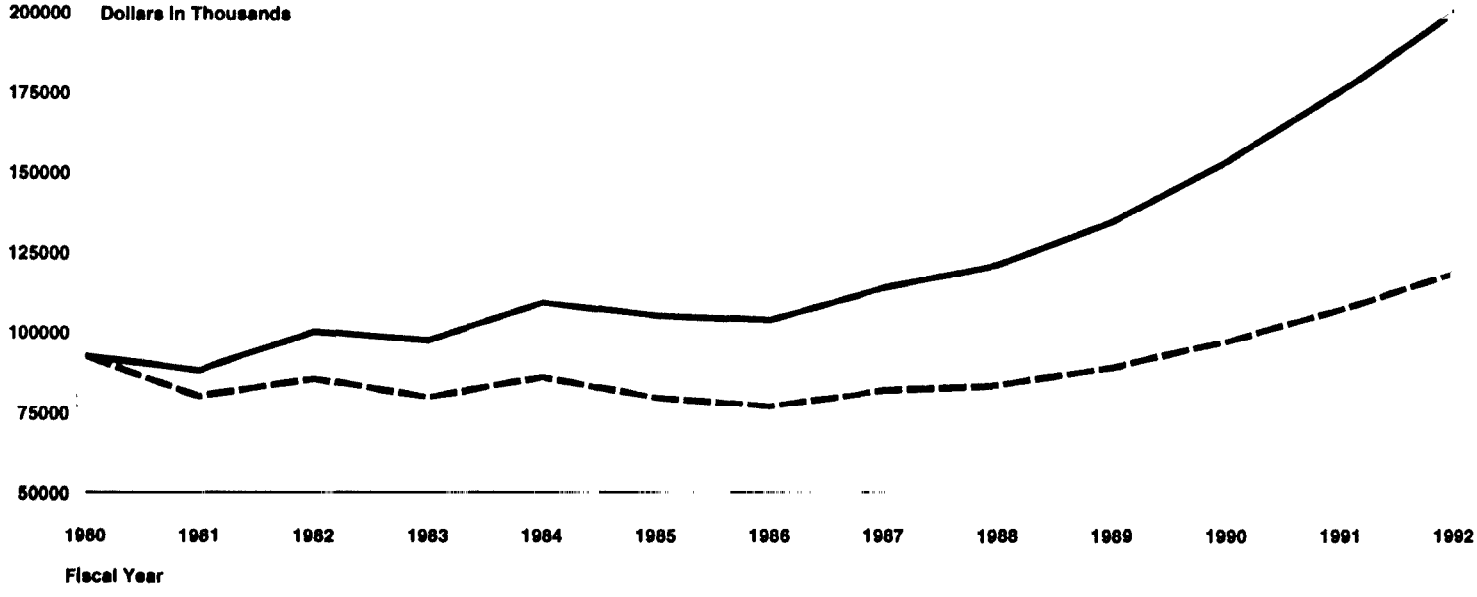
According to FDA officials and others, FDA has had difficulty recruiting and retaining highly qualified scientists and technicians because of competition from industry and others. For example, the new Food Processing and Packaging Strategic Manager told us that because FDA cannot compete with the salaries offered by private industry, FDA has had difficulty attracting new packaging specialists. As a result, FDA does not have the in-house capability to perform the kinds of research necessary to evaluate the safety of new methods of packaging. FDA is aware that it lacks expertise in several scientific disciplines, particularly in food science and technology. FDA is trying to build this expertise in food-processing and food-packaging technologies at the National Center, discussed above, and has asked its newly formed Food Advisory Committee for advice on recruiting and retaining scientists.

During 1990, FDA conducted a comprehensive assessment to determine what resources it would need to accomplish its mission through 1997. As part of this effort, FDA assessed the impacts of several forces shaping its future, including the projected increase in new food products, especially in those developed through new biotechnology. FDA concluded, among other things, that it needed to strengthen its science base to regulate food

products produced by new technologies, such as new biotechnology. CFSAN staff have estimated that over 2,000 staff years and over $215 million above current levels will be needed for expected food safety regulatory activity between 1993 and 1997, including 50 additional staff years to process food petitions related to biotechnology.

Although FDA's budget for food programs has increased in recent years (see fig. VI.1), an FDA official told us that this increase has been largely absorbed by the increasing costs of federal salaries and benefits. In addition, although the number of full-time staff dedicated to food safety programs has increased in recent years (see fig. VI.2) this increase has only restored field staffing to pre-1985 levels and provided some additional staff for the seafood program, according to the FDA official. Furthermore, FDA officials believe that these recent increases in resources have not been sufficient to cover the increasingly complex demands and responsibilities placed on the agency over this same time period. For example, although the Nutrition Labeling and Education Act of 1990 imposed significant new requirements on FDA, the agency did not receive any increase in resources to implement the new law, according to the Acting Senior Associate Director for Policy, Planning, and Strategic Initiatives. Consequently, several food activities, including some responding to new food technologies, were delayed while FDA staff concentrated on meeting the statutory time frames imposed by the new labeling law.

Figure VI.1: FDA's Food Safety Program Funding for Fiscal Years 1980-92

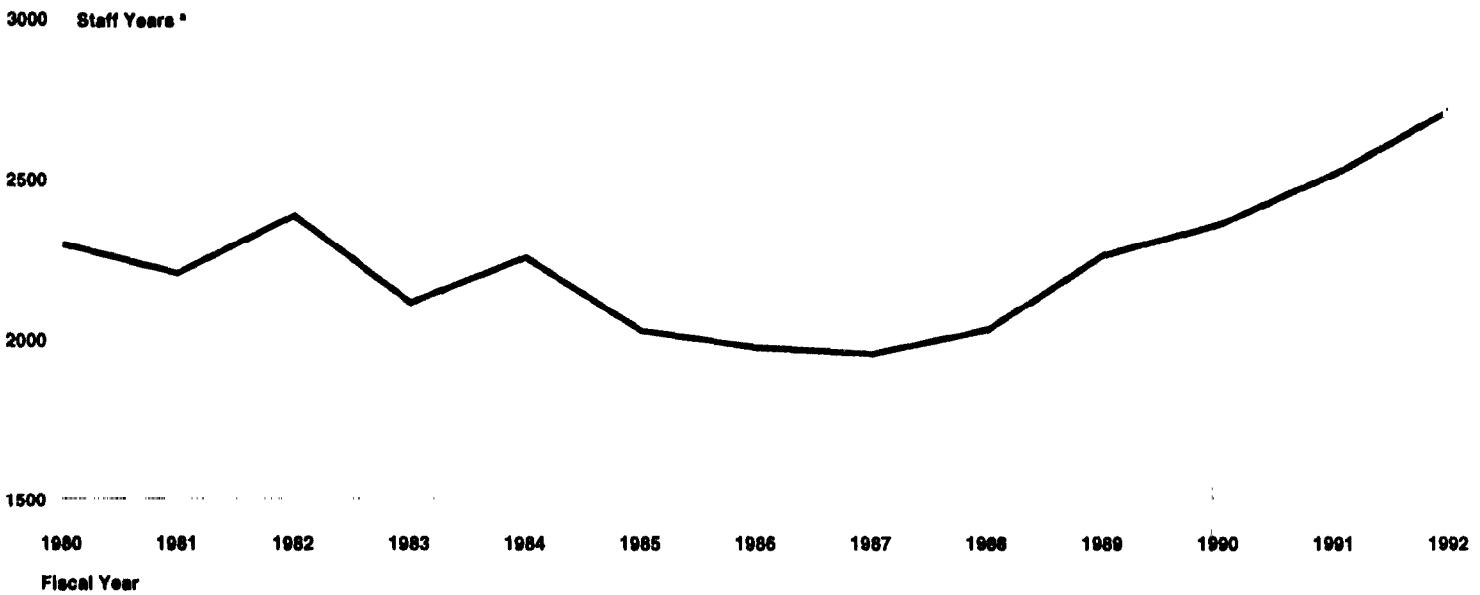


Note: This chart represents funding for the Center for Food Safety and Applied Nutrition and for the Office of Regulatory Affairs.

[a]Adjustment for inflation is based on the gross domestic product deflator figure for 1980, as determined by the Bureau of Economic Analysis, Department of Commerce.

Source: GAO presentation of FDA data.

Figure VI.2: FDA's Food Safety Program Staff Years for Fiscal Years 1980-92



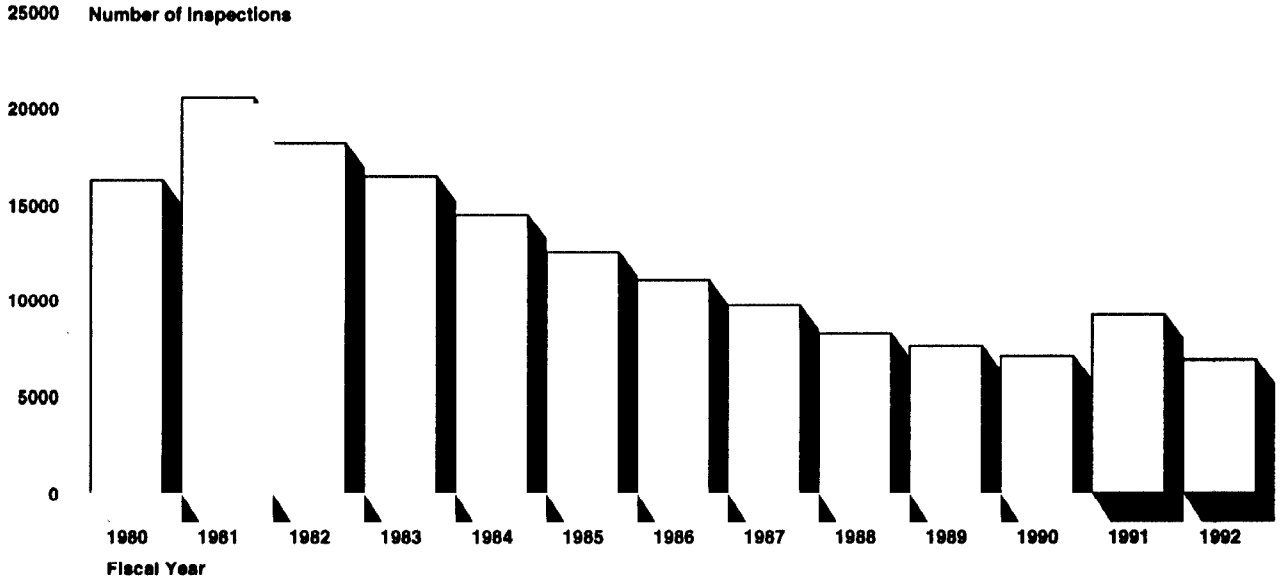
[a]Represents the number of full-time equivalent staff for the Center for Food Safety and Applied Nutrition and for the Office of Regulatory Affairs.

Source: GAO presentation of FDA data.

FDA officials believe that resource constraints have dramatically affected the agency's ability to police the food industry. Even though FDA has recently taken action against certain misbranded food products, the number of inspections of domestic food establishments (e.g., processors, warehouses, etc.) has generally declined over the last 10 years (see fig. VI.3). In contrast, the number of new food products introduced annually to the retail grocery market has more than quadrupled—from just over 2,000 in 1980 to over 12,000 in 1992—and the number and variety of new food products will increase as industry expands its technological capacity. According to FDA officials, FDA has not been able to inspect as many domestic food establishments as it would like because its limited resources have been used to cover emergencies and other higher-priority tasks, such as inspections of blood banks. Because FDA relies to a large extent on postmarket surveillance to ensure the safety of products of new food technologies for consumers, decreasing the number of inspections of domestic food establishments may allow the agency only to respond to food crises rather than to prevent them. As noted above, attempts by FDA

to improve its overall inspection effort by moving to a HACCP approach may be hindered by statutory limitations on the agency's access to manufacturing records.

Figure VI.3: FDA's Inspections of Domestic Food Establishments for Fiscal Years 1980-92



Note: Domestic food establishments include processors and warehouses.

Source: GAO presentation of FDA data.

In recent years, user fees have been considered as a means to help finance FDA's food programs. For example, although the Advisory Committee on the Food and Drug Administration did not take a position on any specific proposal for augmenting FDA's funding, it recommended considering alternative sources of funding for FDA, including user fees. The Committee also stated that any alternative source of funding for FDA should (1) supplement—not serve as a substitute for—an adequate base of appropriations for the agency and (2) be tied to specific improvements in the agency's functions.

Historically, FDA has imposed user fees for certifying color additives, supervising the destruction and reconditioning of products, and inspecting imported tea, among other things. In the last several years, FDA has requested authority from the Congress to charge user fees for approving new food additives and for other activities. However, the Congress inserted specific language in FDA's annual appropriation acts that prohibited the agency from collecting new user fees without specific authorization.

In 1992, the Congress enacted the Prescription Drug User Fee Act of 1992, which imposed fees for FDA's approval of new prescription drugs. The estimated $325 million to be collected in fees over the next 5 years was designed to supplement FDA's existing resources and significantly expedite the approval of prescription drugs. While these fees will give FDA some relief, no additional funding is available for FDA's food programs. FDA staff are working on a proposal to extend user fees to FDA's food programs, including fees for approving new food additives, registering food establishments, and inspecting imported food.

Concerns About FDA's Operations in a Global Economy

The rapid globalization of the food industry has created an environment in which the volume of exotic, imported foods has increased dramatically, together with the need to evaluate their safety. FDA estimates that about $16 billion worth of imported food subject to FDA regulation enters the United States annually.

Because FDA does not have the authority to inspect foreign food establishments, it must inspect imported food products at the port of entry. However, as we have reported in the past, because of resource constraints and other factors, the agency is able to examine only a small percentage of all imported food. Furthermore, the type and composition of imported food has changed, making it more difficult for FDA to examine the safety of the end product that is imported, according to FDA officials. In earlier reports, we have identified other problems with FDA's import program, including the agency's inability to deter the distribution of contaminated food imports.[5]

Some scientists are also concerned about whether FDA can safely regulate imported foods produced by new technologies because these products, unless clearly labeled, may be indistinguishable from traditional products.

[5]See Pesticides: Adulterated Imported Foods Are Reaching U.S. Grocery Shelves (GAO/RCED-92-205, Sept. 24, 1992).

For example, as explained in appendix II, it may not be possible to determine whether a food item has been genetically engineered. According to a 1990 internal FDA report, many advances in food technology are originating outside the United States. Therefore, it is reasonable to assume that some products of new food technologies are imported into the United States. In addition, according to some food scientists, food safety regulation in some countries is not as stringent as in the United States, and products of new technology may not have been evaluated against the same standards as U.S. products. For example, imported products may contain microbes not commonly found in U.S. food products.

We and others have recognized the significant increase in the volume of food imports and the limitations of trying to protect public health by inspecting end products. We have also reported that certification programs, such as one for soft cheese from France, allow FDA to supplement its own inspection efforts by encouraging a foreign government to ensure that products exported to the United States are safe. Certification agreements provide FDA with a mechanism for ensuring that foreign establishments exporting food to the United States use good manufacturing processes similar to those required for domestic establishments. However, we were concerned that such agreements might become mere paper exercises if not actively monitored, and we therefore recommended that FDA develop a formal monitoring program for its certification programs.

Limitations in FDA's ability to oversee the imported products of new food technologies may not only compromise food safety but also place domestic firms at a competitive disadvantage because they may be held to higher standards than FDA is able to impose on foreign firms. Ultimately, FDA's regulation of new food technologies also has implications for the competitiveness of domestic firms and for efforts to harmonize U.S. food safety standards with those of the nation's trading partners.

Objectives, Scope, and Methodology

To develop information on the complex and controversial issues associated with new food technologies, the Chairman, Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce, asked us to

- identify and describe selected new food technologies,
- determine FDA's response to these technologies and review the processes that the agency uses to determine whether they are safe for consumers, and
- identify any unresolved regulatory issues associated with FDA's regulation of new food technologies.

To identify and describe new food technologies and identify any unresolved regulatory issues associated with new food technologies, we interviewed recognized food safety experts and representatives from diverse organizations and perspectives. We used a "snowballing" methodological approach to identify recognized experts in the fields of new food technologies.[1]

We interviewed FDA officials from the Office of Biotechnology, Office of General Counsel, Office of Regulatory Affairs, Office of Consumer Affairs, Office of Planning and Evaluation, Office of the Commissioner, Center for Veterinary Medicine, and many of the offices and divisions within the Center for Food Safety and Applied Nutrition (CFSAN). We visited and interviewed officials from the National Center for Food Safety and Technology, a cooperative research and education endeavor of FDA, academia, and industry in Chicago, Illinois. We interviewed academics, including food scientists at the Food Research Institute at the University of Wisconsin, the Illinois Institute of Technology, the Rutgers University Center for Advanced Food Technology, and the Departments of Food Science at the University of Massachusetts and Purdue University. In addition, we contacted selected state officials, as well as scientists from the Institute of Food Technologists, the International Life Sciences Institute, and the National Academy of Sciences. We interviewed and obtained documents from industry officials and from industry trade associations, including the Food Marketing Institute; the Grocery Manufacturers of America, Inc.; the National Cattlemen's Association; the National Food Processors Association; the Society of the Plastic Industry, Inc.; the United Fresh Fruit and Vegetable Association; and selected firms. We also interviewed representatives from consumer and environmental

[1]In the snowballing technique, each interviewee is asked to identify individuals who he/she believes should be included in a survey.

groups active in new food technology issues, including the Center for Science in the Public Interest, the Consumers Union, the Environmental Defense Fund, the Foundation on Economic Trends, the National Wildlife Federation, and the Public Voice for Food and Health Policy. We also attended several conferences and symposia related to new food technologies.

In addition to interviews, we conducted several literature searches. We reviewed previous reports from GAO, OTA, the Congressional Research Service, and FDA. We identified several reports and studies on new food technologies from organizations, such as the International Food Biotechnology Council and the Advisory Committee on the Food and Drug Administration. We used information and publications from USDA, including the Economic Research Service and other offices; from the Department of Commerce (Commerce), including the Office of Patents and Trademarks and the Bureau of Census; and from industry to identify trends and market forces in the food industry. For information on diet and health trends, we used statistical information and reports from several agencies within the Department of Health and Human Services, including the Centers for Disease Control and Prevention, the National Center for Health Statistics, the Office of the Surgeon General, and the National Research Council.

From the information that we had collected from interviews, literature searches, and previous reports, we determined that although there was no general agreement on what constituted a "new food technology," there were many issues associated with a variety of new food technologies and products. To help focus on specific new food technologies and related issues, we prepared a preliminary observation paper and obtained comments on it from FDA officials and selected industry and consumer representatives. From this work, we selected examples of specific technologies for which (1) products were new to the marketplace/consumer, (2) regulatory issues were unresolved, and (3) FDA had jurisdiction and played the lead role in ensuring the new products' safety. In addition, we tried to select examples that would cover the range of foods, food ingredients, and food processes subject to FDA's regulation. We did not attempt to identify and discuss every new food technology or resolve the scientific controversies over the food safety issues related to new food technologies. Because there is no consensus on what constitutes a new food technology, we cannot claim that the examples we have selected are representative of all new food technologies. They are,

however, illustrative of the many complex issues raised by various types of new food technologies.

To determine FDA's responses to and processes for regulating new food technologies, we interviewed FDA officials, and we collected and analyzed standard operating procedures, policy statements, internal memorandums, speeches, journal articles, and reports on emerging food technologies from FDA offices. We reviewed selected FDA food additive and generally recognized as safe (GRAS) petition files. To describe FDA's existing statutory authority and processes for regulating food and food ingredients, including the products of new technologies, we reviewed the provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended, as well as other major acts governing FDA activities, the Code of Federal Regulations, and relevant Federal Register notices. We also attended training courses sponsored by FDA and the Food and Drug Law Institute on federal food laws and regulations. To determine how and to what extent FDA plans for and anticipates new food technologies, we interviewed officials from the Office of Planning and Evaluation, FDA, and from CFSAN. We also gathered and analyzed pertinent planning calendars and technical plans.

To identify the food safety responsibilities of federal agencies other than FDA and determine their relationship to FDA with respect to the regulation of new food technologies, we interviewed several officials from agencies within USDA, the Environmental Protection Agency, and Commerce.

We conducted our initial review from November 1990 to October 1991 and briefed the Chairman's office on the preliminary results of our work in October 1991. Subsequently, as arranged with the Chairman's office, we suspended work on the review to complete other work on food safety requested by the Chairman and by other Subcommittee chairs. We reactivated the review in February 1993 after updating information with FDA officials and selected nongovernmental organizations. We performed our work in accordance with generally accepted government auditing standards.

We discussed the information in this report with officials in FDA's Center for Food Safety and Applied Nutrition, Center for Veterinary Medicine, Office of Regulatory Affairs, Office of General Counsel, and Office of the Commissioner, including CFSAN's Deputy Director for Programs, and have included their comments where appropriate. FDA officials generally agreed with the accuracy and completeness of the facts presented. However, as

requested, we did not obtain written agency comments on a draft of this report.

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