CCFL

AGENDA ITEM 5

SOUTH AFRICA

APPENDIX II

FDA'S Policy for Foods Developed by Biotechnology

U. S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
http://vm.cfsan.fda.gov/~lrd/biopolcy.html

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Abstract

The Food and Drug Administration (FDA) has authority under the Federal Food, Drug, and Cosmetic Act (the Act) to ensure the safety and wholesomeness of most foods, except meat and poultry, including foods developed through modern biotechnology. In 1990, FDA issued the first regulation for the use of a recombinant DNA-produced food ingredient, fermentation-derived chymosin (rennet). In 1992, FDA published a policy statement that explains how foods and animal feeds derived from new plant varieties developed by both conventional and new breeding techniques are regulated under the Act. The 1992 policy

provides "guidance to industry" that established a standard of care for assuring safety and wholesomeness. This discussion will summarize FDA's policy and illustrate how the policy was applied by the agency in reaching decisions on chymosin and on the Flavr Savr tomato.

Introduction

Foods and food ingredients produced through the techniques of modern molecular biology are now a reality. Over the past four years, FDA has approved the commercial use of chymosin (rennet) produced from bacteria (1-2), yeast (3), and fungi (4) for use in making cheese and other dairy products. Earlier this year, FDA determined that the Flavr Savr tomato developed by Calgene, Inc. was as safe as other commercial tomatoes (5). Over forty food crops modified via recombinant DNA techniques are expected to reach the market in the near future. These crops exhibit improved shelf-life, processing characteristics, flavor, nutritional properties, and agronomic characteristics, such as tolerance to chemical herbicides and resistance to pests and disease.

Recombinant DNA techniques are methods of molecular biology that permit scientists to identify specific genes, make copies of those genes, and introduce the gene copies into recipient organisms, such as a food crop or a microbial starter culture. Once incorporated into the host genome, the introduced gene functions like all other genes in the genome. This process is called transformation, and it is commonly referred to as genetic engineering or gene splicing. Using these techniques, scientists can make copies of genes from any organism--plant, animal, or microbe--from which a potentially useful trait can be identified.

These new methods of gene transfer have greatly expanded the pool of potentially useful traits available to scientists for improving food source organisms. Because recombinant DNA techniques are used to introduce one or a few genes into an organism such as a food crop, agricultural scientists avoid one of the major difficulties of conventional cross hybridization, the concomitant introduction of undesirable genes closely linked to the trait of interest and the subsequent back-crossing necessary to eliminate undesired traits.

The power of genetic modification techniques, in terms of specificity and potentially useful traits, has increased as new methods of gene transfer have been developed (6). Cross-hybridization involves recombination of thousands of genes on whole chromosomes, while recombinant DNA techniques are used to transfer or modify one or a

few well-characterized genes. Recombinant DNA techniques are used to achieve the same goals that developers have sought through other methods of genetic modification. As such these methods are research tools available to developers for strain and varietal improvement programs and may be used in conjunction with cross-hybridization, chemical and radiation mutagenesis, somaclonal variation, and embryo rescue to improve crops.

In spite of the technical advantages of using recombinant DNA techniques, questions have been raised concerning the safety of foods derived using these techniques, especially with respect to the ability to introduce a gene into a food source organism from any source. For example, concern is often expressed that new substances whose safety has not been established will be introduced into food, or that unexpected or unintended effects will occur as a result of the newly introduced genetic material, or that new allergens may be present in the food.

FDA's Role in Assuring Food Safety

The public relies on FDA for assurance that foods are safe and wholesome. FDA has authority under the Act, to ensure the safety of most domestic and imported foods in the U.S. market, except meat and poultry which are regulated by the U.S. Department of Agriculture (USDA). Pesticides used in or on foods are regulated primarily by the Environmental Protection Agency (EPA), which reviews safety and sets tolerances (or establishes exemptions from tolerance) for pesticides. FDA monitors foods to enforce the tolerances for pesticides set by EPA.

FDA regulates foods and food ingredients developed by genetic engineering by the same provisions and regulations under the Act that it regulates other food products. This means that a food or food ingredient developed by genetic engineering must meet the same rigorous safety standards under the Act as other food products, and FDA has broad authority to take legal action against a substance that poses a hazard to the public.

Chymosin: The First Biotechnology-Derived Food Ingredient
In March 1990, FDA issued the first regulation in the U.S. for the use in food of a substance produced by recombinant DNA techniques (see references 1-2). This substance, chymosin (rennet), is the milk-clotting enzyme used to make cheese and other dairy products. FDA affirmed that chymosin was "generally recognized as safe" (GRAS), meaning that it is exempt from the premarket approval requirements that apply to new food additives. The source of the new enzyme was

E. Coli K-12. Subsequently, chymosin preparations produced from Kluyveromyces marxianus var. lactis and Aspergillus niger var. awamori were also affirmed as GRAS (see references 3-4).

Several factors were important in FDA's approval of fermentation produced chymosin: the introduced chymosin gene encoded a protein that had the same structure and function as animal-derived chymosin; the manufacturing process removes most impurities; the production microorganisms are destroyed or removed during processing and are non-toxigenic and non-pathogenic; and any antibiotic-resistance marker genes (e.g., ampicillin) are destroyed in the manufacturing process.

FDA's Policy for Foods Derived from New Plant Varieties

FDA has on occasion been asked questions regarding the safety of new plant varieties, and in the mid-1970s the agency considered criteria by which it would review new varieties developed through conventional breeding (7). It was recognized that nutrients and toxicants were important indicators of safety. Following the development of molecular biology techniques that could be used to genetically modify food crops in very specific ways, FDA received many questions from developers concerning the safety and regulatory status of these new foods.

In 1992, FDA published and invited public comment on a policy statement (the 1992 policy) clarifying its legal and regulatory framework for oversight of food and animal feed derived from new plant varieties developed by both conventional and new breeding techniques, such as recombinant DNA techniques (8). FDA published the 1992 policy to ensure that guidance concerning food safety and regulatory issues was available to developers before products developed by recombinant DNA methods would be ready for safety testing. FDA's policy explains how whole foods, including animal feeds, derived from fruits, vegetables, grains, and by-products such as vegetable oils and food starch are regulated under the Act. The policy covers foods derived from plants developed through all methods of breeding, including genetic engineering. While we requested public comment on our policy, the 1992 policy is our working policy. We feel that our policy for a rapidly evolving technology, such as recombinant DNA techniques, should be one which is sufficiently flexible to permit necessary modifications as a result of technological innovations or other information that may come to our attention. For example, we are continuing to consider issues raised in comments regarding allergenicity, labeling, and premarket notification.

FDA relies primarily on two sections of the Act to ensure the safety of foods and food ingredients. Generally, whole foods, such as fruits, vegetables, and grains, are not subject to premarket approval. The primary legal tool that FDA has successfully used to ensure the safety of foods is the adulteration provisions of section 402(a)(1). The Act places a legal duty on developers to ensure that the foods they present to consumers are safe and comply with all legal requirements. FDA has authority to remove a food from the market if it poses a risk to public health. Foods derived from new plant varieties developed through genetic engineering will be regulated under this authority as well.

The second section of the Act that FDA relies on is the food additive provision (section 409). Under this section, substances that are intentionally added to food are food additives, unless the substance is generally recognized as safe (GRAS). Food additives are subject to review and approval by FDA before they may be used in food. When requested to do so, FDA also reviews and affirms the GRAS status of food ingredients when there is a question regarding the regulatory status of a substance intended for use in food. I discuss below how this premarket authority will apply to genetic modifications in food crops.

The centerpiece of our 1992 policy statement is a comprehensive "guidance to industry" section that discusses scientific issues for assuring safety and identifies scientific and regulatory questions for which firms should consult with FDA. Our guidance to industry establishes a "standard of care" for developers to ensure food safety. The scientific principles that underpin FDA's 1992 policy have been published (9). These principles are consistent with the principles for safety assessment discussed by various prestigious organizations, including the National Research Council in the U.S. (10, see reference 6), the World Health Organization and the Food and Agriculture Organization of the United Nations (11), and the Organization for Economic Cooperation and Development (12).

Our approach to assessing safety and nutritional composition of a food derived from a new plant variety is predicated on several considerations (13). Today, our grocery stores exhibit a diversity of foods derived from literally hundreds of genetically distinct, new plant varieties, whose safety has been accepted primarily through experience. Rigorous scientific analysis using analytical chemical methods or toxicological studies in animals are rarely conducted. For example, solanine, a glycoalkaloid native to potatoes, is one of the few

toxicants in food crops monitored by vegetable breeders in the U.S. Based upon the extensive history of safety of plant varieties developed through agricultural research, FDA has not found it necessary to review the safety of foods derived from new plant varieties.

We consider the foods that we have today to be the standard by which the safety of foods derived from new plant varieties should be compared (see references 11-13). The safety assessment approach outlined in our 1992 policy focuses on the intended genetic modification and the overall composition of important nutrients and toxicants in the food. This concept recognizes that the new foods are variants of existing, well-accepted foods and that foods are not inherently safe. That is, many foods contain components that would present safety concerns if those substances were present in the food in concentrations above the range that has been found to be acceptable. In addition, some individuals in the population are allergic or intolerant to certain foods. Thus, a level of absolute safety for a food cannot be achieved or expected.

Rather, it is widely accepted in the scientific community that a food derived from a new plant variety should be evaluated relative to other commercial varieties of the crop. It is also recognized that foods--fruits, vegetables, and grains--consist of complex mixtures of many substances. The accepted approach for assessing safety of foods differs from approaches applied to single chemical substances such as food additives and pesticides whose safety is generally established by non-clinical studies in animals. Animal feeding studies with foods are usually not sufficiently sensitive to detect toxic constituents in the food, and it is usually not possible to supplement the diet with a high enough concentration of test material to achieve the desired safety margin. In addition, high concentrations of food added to the diet can perturb the nutritional balance of the diet and confound interpretation of the results.

To circumvent the difficulties of tests in animals, a multi-disciplinary approach is used to evaluate the safety and nutritional composition of a food. This approach relies on information pertaining to the agronomic and quality attributes of the plant, genetic analysis of the modification and stability of expected genomic traits (e.g. Southern analysis of the introduced gene(s) and restriction fragment length polymorphisms), evaluation of the safety (toxicity and allergenicity) of newly introduced proteins, and chemical analyses of important toxicants and nutrients. If a safety question remains after this

evaluation, toxicological studies can be designed to address remaining questions.

The guidance to industry section of the 1992 policy focuses on issues related to changes in food crops that are both intended and unintended or unexpected modifications of the finished food. We begin with the premise that many varieties of food crops have been developed through plant breeding and that the foods derived from these varieties are generally safe for consumption, although there have been rare exceptions. Our guidance addresses relevant safety issues with respect to the food crop that is being modified, the potential for any introduced genetic material to encode harmful substances, the safety of intentionally introduced substances (e.g., proteins encoded by introduced genes), and the assessment of acceptable levels of known plant toxicants and important nutrients in the new variety. This guidance is presented in a series of flow charts and text that covers the food crop being modified, the source(s) of any introduced genetic material, and new substances intentionally added to the food as a result of the genetic modification, i.e., proteins, fatty acids, and carbohydrates.

One important feature of the 1992 policy is that we will require premarket approval as food additives for proteins (or other added substances such as fatty acids and carbohydrates) produced by introduced genes if the protein differs substantially in structure and function from the many proteins that comprise our foods. Conversely, we will presume that proteins that are derived from foods and proteins that are substantially similar to such proteins are GRAS. In these cases, premarket review is generally not required. Based on our present knowledge of developments in agricultural research, we believe that most of the substances that are being introduced into food by genetic modification have been safely consumed as food or are substantially similar to such substances. Therefore, we do not anticipate that most foods developed by recombinant DNA methods will contain substances that require premarket approval as new food additives.

One issue related to the transfer of genetic material between organisms that we believe deserves particular attention is the possibility that proteins that have been introduced into a food could cause allergic reactions in some individuals. We believe that particular attention should be given to proteins that are derived from foods to which individuals in the U.S. population are commonly allergic, such as milk, eggs, wheat, fish, tree nuts, and legumes. In such cases, the

developer should demonstrate scientifically that the allergenic substance is not present in the new food, or FDA would require some form of labeling to alert sensitive consumers.

In April, 1994, FDA, EPA, and USDA hosted a scientific conference on "Scientific Issues Related to Potential Allergenicity in Transgenic Food Crops" (14, transcript available from FDA Docket No. 94N-0053). The goal of the conference was to foster a dialogue among scientists on food allergy and new varieties of food crops developed by gene transfer to assess current information regarding the attributes of substances (such as proteins) that are food allergens. The scientists presented and discussed papers on plant breeding and biotechnology, allergenic foods, exposure and allergic response, T cell and B cell antigenic determinants, in vitro and in vivo diagnostics, and animal models. They noted that allergic reactions to foods occur in a small percentage of the U.S. population, but nevertheless, affect a significant number of individuals. Life threatening reactions are a rare occurrence, and most allergic reactions to foods can be attributed to fewer than a dozen foods. Methods are available to assess allergenic potential for proteins that are derived from sources to which consumers have reacted and for which serum is available, but it may be useful to establish a serum bank. There are no direct methods to assess potential allergenicity of proteins from sources that are not known to produce food allergy. Although some assurance can be provided to minimize the possibility that a new protein will cause an allergic reaction by evaluating its similarity with characteristics of known food allergens (i.e., whether the new protein has a molecular size and a similar amino acid sequence to known allergens and whether the new protein is resistant to degradation by heat, acid, and gastric enzymes), no one factor is predictive. Glycosylation of the protein was not considered a useful parameter.

The goal of a safety and nutritional assessment should be to establish that the new food is as safe as the foods in our grocery stores today. As we have said previously (see reference 9), "FDA's science-based approach for ensuring the safety of foods from new plant varieties focuses safety evaluation on the objective characteristics of the food: The safety of any newly introduced substances and any unintended increased concentrations of toxicants beyond the range known to be safe in food or alterations of important nutrients that may occur as a result of genetic modification. Substances that have a safe history of use in food and substances that are substantially similar to such substances generally would not require extensive premarket safety testing. Substances that raise safety concerns would be subjected to

closer inquiry. This approach is both scientifically and legally sound and should be adequate to fully protect public health while not inhibiting innovation."

Evaluation of the Flavr Savr Tomato

The first food derived from a crop modified via recombinant DNA techniques to come before FDA was the Flavr Savr tomato developed by Calgene, Inc. (Calgene) of Davis, California (15-16, see also FDA Docket No. 91A-0330). To develop this tomato, Calgene used recombinant DNA techniques to introduce an antisense polygalacturonase (PG) gene into the tomato. The sense PG gene, normally present in tomatoes, encodes the enzyme PG, which is associated with the breakdown of pectin (a constituent of the tomato cell wall) and the resulting softening of ripe tomatoes. The antisense PG encodes a messenger RNA that suppresses the production of the PG enzyme. The result is a tomato that remains on the vine longer for enhanced flavor.

In developing the Flavr Savr tomato, Calgene used a selectable marker gene, kanamycin resistance, that encodes the enzyme, aminoglycoside-3'-phosphotransferase II (APH (3')II), to identify plant cells carrying the antisense PG gene. APH (3')II inactivates the antibiotics kanamycin and neomycin, and its presence in plant cells permits cells to survive and grow in the presence of these antibiotics, unlike normal plant cells which are killed by these antibiotics. This allows scientists to select transformed cells that have successfully taken up the desired PG gene.

Calgene asked FDA to evaluate the Flavr Savr tomato under the most stringent procedures available for foods to ensure public confidence in their product. Thus, in addition to evaluating the firm's safety and nutritional assessment of the tomato per se, Calgene requested that FDA regulate the APH(3')II enzyme, the only new substance in the Flavr Savr tomato, as a food additive (for details see FDA Docket Nos. 90A-0416 and 91A-0330).

Overall, we evaluated the data and information provided by Calgene to determine whether Flavr Savr tomatoes have been significantly altered when compared to varieties of tomatoes with a safe history of use. In other words, we asked, "Are Flavr Savr tomatoes as safe as other currently consumed tomatoes?"

Based on the safety and nutritional assessment described in our 1992 policy and the modifications of the Flavr Savr tomato, we believed that

this new tomato should be addressed by an analysis of the following information: the source, identity, function, and stability of genetic material introduced into Flavr Savr tomatoes; analytical studies on the composition of Flavr Savr tomatoes; and the safety of APH(3')II. We also evaluated the environmental safety of the use of the kanamycin resistance gene as part of our review of the food additive petition for APH(3')II.

The DNA introduced into the Flavr Savr tomato was derived from Agrobacterium tumefaciens, E. coli, cauliflower mosaic virus, and tomato. Calgene demonstrated that APH(3')II was the only full-length gene encoded by the introduced genetic material. The firm also showed that the introduced DNA was stably integrated in the tomato chromosome and remained unchanged over five generations.

Calgene compared the nutritional profile of Flavr Savr tomatoes to the parental variety to ensure that the new tomato did not exhibit unexpected changes in composition. Due to the high consumption of tomatoes and tomato products in the U.S., tomatoes are an important source of vitamins A and C. Calgene analyzed representative fruits for these vitamins during storage under conditions expected for commercial tomatoes. The firm found no significant difference between the Flavr Savr tomato lines and the control parental line. Calgene also found no difference between the Flavr Savr tomato lines and the control parental line in lycopene or beta-carotene content.

Based on our discussions with plant breeders, it is not routine practice for developers to analyze new tomato varieties for the naturally occurring glycoalkaloid, tomatine. However, Calgene wished to provide assurance that unexpectedly high levels of this toxicant did not occur in Flavr Savr tomatoes. Tomatine is known to occur in mature green tomato fruit, and tomatine concentrations decrease as the fruit ripens. Calgene showed that there were no significant differences in the glycoalkaloid content between Flavr Savr tomatoes and commercial tomato varieties at both mature green and red ripe stages of development.

The only new substance introduced into the Flavr Savr tomato was the APH(3')II marker gene protein. General considerations for the safe use of marker genes have been established (17). Calgene evaluated the safety of this protein (18) and showed that APH(3')II is rapidly inactivated by stomach acid and digestive enzymes. The firm also noted that enzymes such as APH(3')II are heat labile. The enzyme also does not have significant homology to any proteins listed as food

allergens or toxins. Further, APH(3')II is a phosphorylating enzyme, a type of enzyme commonly found in edible plants and animals. Finally, the enzyme occurs in food at very low concentrations (conservatively estimated at 0.16 part per million in the diet, based on a 100-percent market share for tomatoes containing APH(3')II). FDA concluded that APH(3')II does not possess any of the recognized characteristics of food allergens or any attributes that would distinguish it toxicologically from other phosphorylating enzymes in food.

Calgene also considered whether APH(3')II could affect the therapeutic efficacy of orally administered aminoglycoside antibiotics. Even though the enzyme had been shown to be rapidly degraded under normal gastric conditions, Calgene evaluated whether a significant amount of orally administered antibiotic could be inactivated by APH(3')II under abnormal stomach conditions, such as may exist in patients treated with drugs that reduce stomach acidity, where the enzyme might survive digestion. APH(3')II requires the cofactor ATP for enzyme activity, and Calgene considered whether the amount of ATP available in food would be sufficient to result in the inactivation of a significant amount of orally administered antibiotic. Calgene's worst-case assessment (high intake of ATP-containing food, low dose of antibiotic) showed that only a small fraction of the antibiotic would be inactivated. The firm also showed that no significant inactivation of kanamycin was observed during in vitro studies on tomato extract containing APH(3')II and kanamycin.

Calgene also considered whether the kanamycin resistance gene present in the Flavr Savr tomato chromosome could be transferred to pathogenic microbes in the intestinal tract or in soil, rendering the microbes refractory to the effects of the antibiotic. There is no known mechanism by which a gene can be transferred from a plant chromosome to a microbe. Thus, the possibility that such transfer would generate new resistant organisms is very small, especially when compared to the high rate of spread of resistance through known mechanisms of microbe-to-microbe transfer of antibiotic resistance genes.

Based on the information that Calgene submitted concerning the Flavr Savr tomato, we concluded that this new variety had not been significantly altered in regard to safety when compared to varieties of tomatoes with a safe history of use. We also concluded that the only new substance in the tomato, APH(3')II, was safe for consumption when present in tomatoes at the concentrations typically found in food derived from plants transformed using this selectable marker.

Labeling

FDA's May 1992 policy addressed the labeling of foods derived from new plant varieties, including plants developed by genetic engineering (see reference 8, p 22991). The Act defines the information that must be disclosed in labeling (including on the food label). The Act requires that all labeling be truthful and not misleading. The Act does not require disclosure in labeling of information solely on the basis of consumers' desire to know. The Act does require that a food be given a common or usual name, and that the label disclose information that is material to representations made or suggested about the product and consequences that may arise from the use of the product.

FDA will require special labeling if the composition of a food developed through genetic engineering or any other method differs significantly from its conventional counterpart. For example, if a food contained a major new sweetener as a result of genetic modification, a new common or usual name or other labeling may be required. Similarly, if a new food contains a protein derived from a food that commonly causes allergic reactions (and the developer cannot demonstrate that the protein is not an allergen) labeling would be necessary to alert sensitive consumers because they would not expect to be allergic to that food. However, if a protein commonly produces very serious allergic reactions (e.g., peanut protein) and is transferred to another food, FDA would need to evaluate whether it would be practicable to label the food throughout its distribution. Circumstances could exist for which labeling would not provide sufficient consumer protection, and FDA would take appropriate steps to ensure that the food would not be marketed.

To date, FDA is not aware of information that would distinguish genetically engineered foods as a class from foods developed through other methods of plant breeding and, thus, require such foods to be specially labeled to disclose the method of development. The agency has not required labeling for other methods of plant breeding such as chemical- or radiation-induced mutagenesis, somaclonal variation, or cell culture. For example, sweet corn is not required to be labeled "hybrid sweet corn" because it was developed through cross-hybridization.

FDA did not require special labeling for the Flavr Savr tomato. We concluded that the correct common or usual name for the Flavr Savr tomato is "tomato", because the new tomato is not significantly different from the range of commercial varieties referred to by that

name. However, Calgene has decided to provide special labeling, including point of sale information, to inform consumers that the new tomato has been developed through genetic engineering (see reference 5).

Summary

Irrespective of the method by which a food or food ingredient is produced, all products must meet the same stringent safety standards and be properly labeled in accordance with the Act. Our approval of fermentation-produced chymosin illustrated an approach for assessing safety of substances derived from genetically modified sources. FDA has since provided guidance for developers that establishes a standard of care to ensure that foods derived from new plant varieties are safe and wholesome. FDA evaluated the data and information supplied by Calgene and agreed with the firm that the Flavr Savr tomato is as safe as other commonly consumed tomatoes.

Postscript

Since our decision on the Flavr Savr tomato, we have asked developers of foods derived from new plant varieties developed using recombinant DNA techniques to provide only summary information of their safety and nutritional assessment to FDA and to make a scientific presentation of their data to our scientists. This informal notification process serves to inform the agency about developments in the technology and permits us to identify any unresolved safety or regulatory questions. In November 1994, FDA completed informal notifications with developers on seven additional foods derived from plants modified via recombinant DNA techniques, and presented the safety and nutritional summary information on the products to the agency's Food Advisory Committee. These foods included: delayed ripening tomatoes (DNA Plant Technology, Monsanto, Co., and Zeneca Plant Sciences); pest resistant crops: virus-resistant squash (Asgrow Seed Co.), and Colorado potato beetle-resistant potato (Monsanto, Co.); herbicide-tolerant crops: bromoxynil-tolerant cotton (Calgene, Inc.), and glyphosate-tolerant soybean (Monsanto Co.). The FAC agreed with FDA that there are no outstanding food safety issues associated with these products.

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