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# *Ensuring Food and Feed Safety: US Food Law and FDA's Biotechnology Consultation Process*

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A key aspect of the authority for regulating genetically engineered crops is the legal basis of that authority. For example, in contrast to what some people think, the Food and Drug Administration (FDA) cannot make consultation mandatory, because there is no law to permit it. In 1992, FDA published an article in the *Federal Register—The Statement of Policy: Foods Derived from New Plant Varieties*—in which was discussed its legal framework for considering new plant varieties as a whole, including genetically engineered varieties. The article's focus was chiefly on elements already in the Food, Drug, and Cosmetic Act (FD&C Act), and it explained the agency's thinking about safety and regulatory issues pertaining to new plant varieties, based on several parts of existing food law.

The first issue is adulteration, the second is food additives, and the third is labeling (Figure 1). There are two basic elements to US food law. The first is the responsibility of purveyors—which include crop developers, farmers, and manufacturers—to ensure that the foods they market are safe, wholesome, and comply with all applicable legal and regulatory requirements. The second element is what FDA does to enforce the law, using regulatory tools to remove unsafe or illegal foods and ingredients from the marketplace. These include seizures, recalls, and denial of entry of food from abroad.

We have a program to help developers ensure that food from new plant varieties is safe and complies with laws and regulations. Three legal requirements are applicable.

- Safety: The food is as safe as that generated from traditionally bred varieties.
- Labeling: The food labeling is truthful and not misleading.”
- Additives: Is premarket review required?

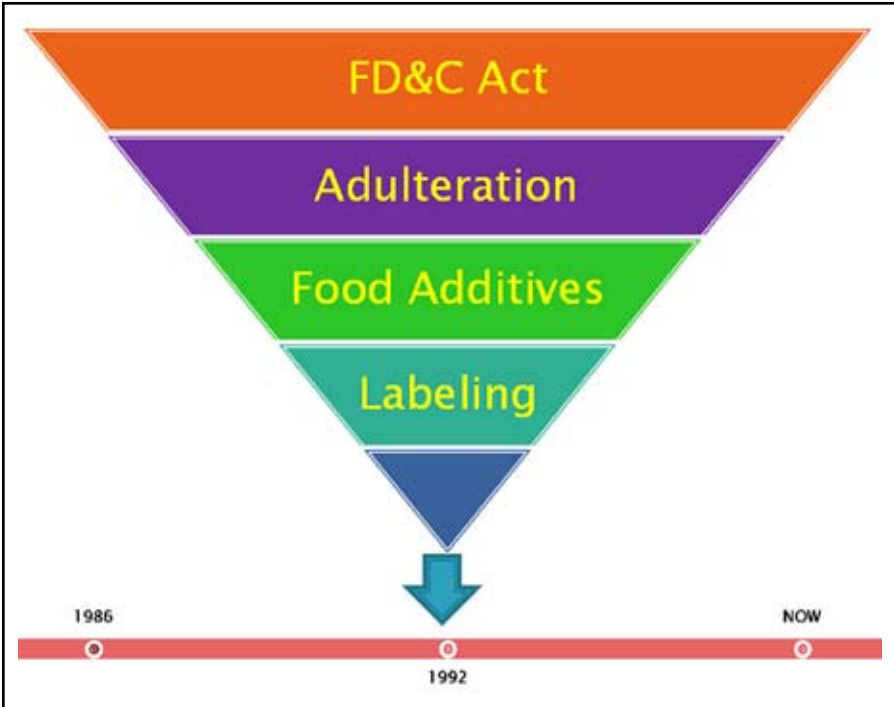


Figure 1. FDA's legal framework for foods from new plant varieties.

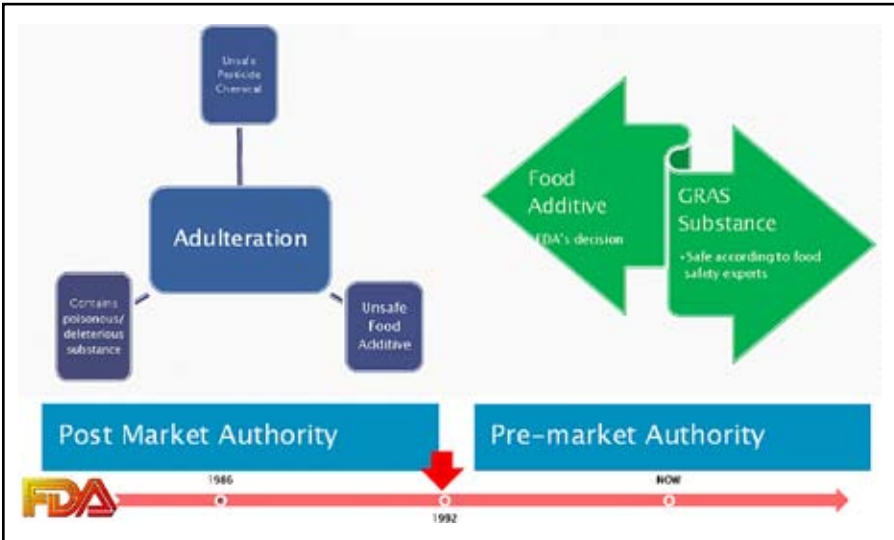


Figure 2. FDA's authority: the FD&C Act.

## FDA'S AUTHORITY

There are two basic elements to FDA's authority. The first is post-market authority (Figure 2), under the adulteration provision of the FD&C Act, which, generally, applies to whole foods. A food is considered adulterated if it contains a poisonous or otherwise deleterious substance known to harm humans or animals, if it contains an unsafe food additive, or if it contains an unsafe pesticidal chemical. The second element is FDA's premarket authority governing food additives, unless data show that they are generally recognized as safe ("GRAS") by qualified experts in their intended use.

Under what circumstances would a food additive be present in a genetically engineered plant? It would be a new protein or the product of a new protein for which safety information is not publicly available or widely accepted. Accordingly, FDA would require a review before marketing. So far, the only example of a food additive in a genetically engineered plant was the NPTII enzyme used as a selective marker in the FlavrSavr tomato. At the time Calgene submitted its food-additive petition, there was no experience with using proteins of this type in food.

## LABELING

According to the "misbranding" part of the FD&C Act, a label on a food must be truthful and not misleading. A label must be changed if a meaningful difference is created by conferring a change in a food; it must be called something different. To date, the best examples are modified oil crops, *e.g.* high oleic acid soybean and stearidonic acid soybean.

## 1992 POLICY

In summary, the 1992 policy considers whether the product in question is as safe as other foods. It provided guidance to industry via decision trees and includes a suggestion that developers consult with FDA early in the development process, so that potential issues may be identified before they become problems.

## CFSAN AND CVM

Submissions to FDA are evaluated by two centers for different uses. Safety of use in human food is evaluated by the Center for Food Safety and Applied Nutrition (CFSAN), whereas the Center for Veterinary Medicine (CVM) evaluates safety of use in animal feed. Again, we advise early consultations at FDA to advise us of what you are doing, then return to the lab to run tests for potential toxicity, allergenicity and antinutrient content, and potential for bioavailability alteration. This is followed by submission of a dossier—hopefully not too lengthy—describing why the use of the plant as food or would be safe and legal.

What are the issues? Regarding safety, there's the potential for toxicity, the potential for allergenicity, and for changes in levels of anti-nutrients and in bioavailability. Regarding regulatory considerations, there's the question of whether a new substance is an unapproved food additive or GRAS, or whether there's a meaningful change requiring a new common or usual name.

In essence, we ask people to tell us their story—about their new plant variety and why it's safe for food use. As for FDA's role, we recognize that there's widespread variation in plants in nature, including among domesticated varieties, affected by environmental conditions and the genetic background (Figure 3). We have developed a process whereby we evaluate final submissions and if there are aspects we don't understand, we will seek clarification. We then develop our own document, and conclude by sending a letter. We mail the letter to the submitter and place a memo on our website—a scientific evaluation that establishes whether the new variety is as safe as those already in the marketplace.

We added a new piece in 2006. When preparing for field trials with a protein that hasn't been used before, our early food-safety evaluation (Figure 4) is worthy of consideration. This guidance is termed a "new protein consultation" (NPC). If a new protein is neither toxic nor allergenic, then it would be considered safe for field testing and FDA would not be concerned if low levels appeared inadvertently in the marketplace.

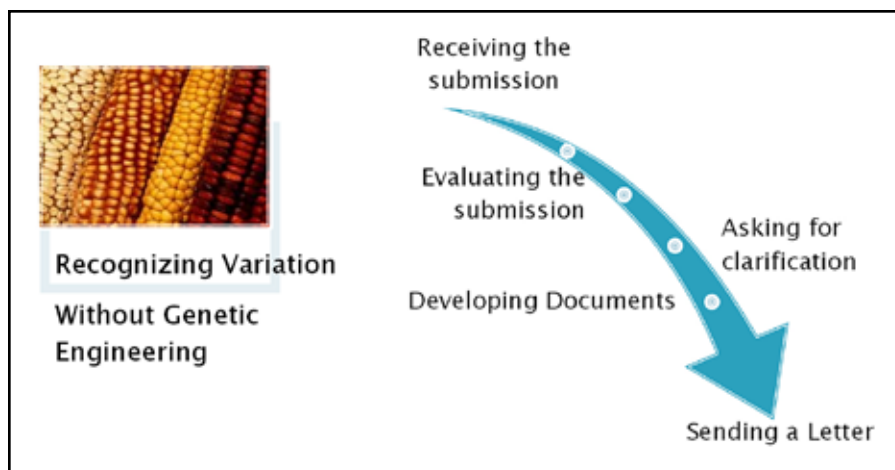


Figure 3. Consultation procedures: FDA's role.

## SAFETY ASSESSMENT

As far as safety assessment is concerned, we understand that agronomic and quality issues will eliminate some lines from consideration at the very beginning of the process (Figure 5). We need to have information on new substances, including identity and source, using the weight-of-evidence approach. And we need to look at composition, and perhaps at some agronomic aspects. The intended effects must be clarified in terms of overall effects on the food and compositional changes. And, finally, unintended effects may be important. Does the insertion result in expression of (a) new or altered protein(s), or even fusion proteins? Are there unanticipated actions of a new enzyme on other components within the plant?

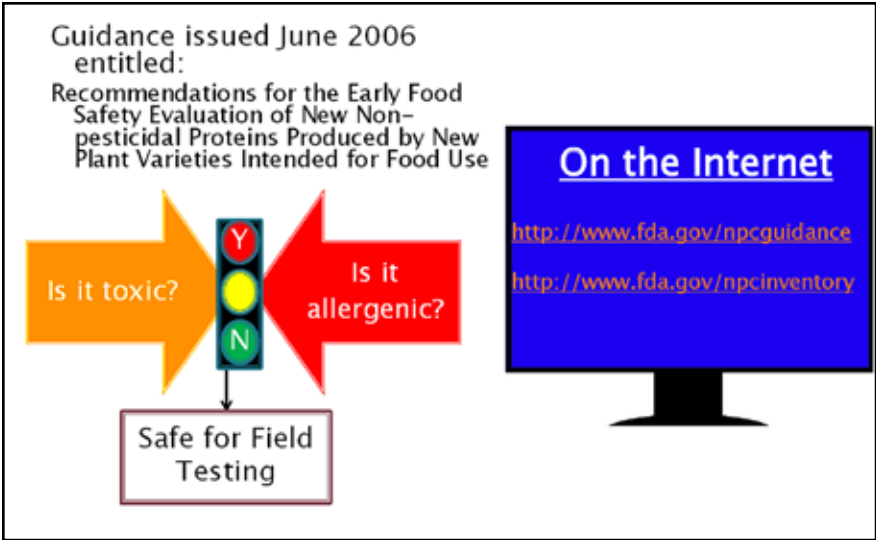


Figure 4. Early food-safety evaluations (NPCs).

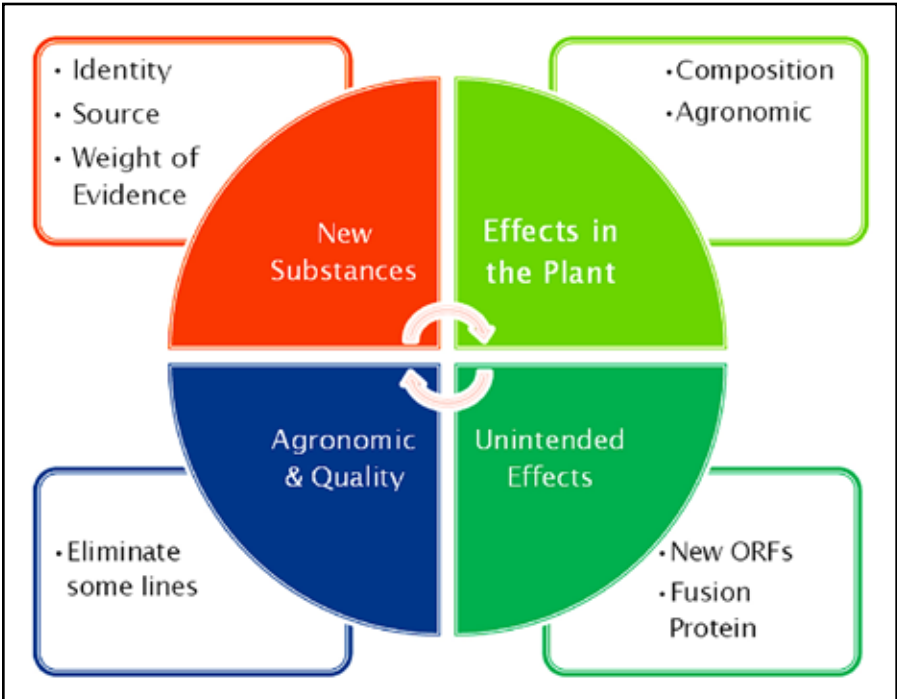


Figure 5. Safety assessment-1.

For safety assessments, three basic components are applicable (Figure 6). Genetic analysis focuses on stability and unintended effects. Chemical and nutritional analyses focus on dietary impacts and toxicant levels. And allergenicity and, to a lesser degree, toxicity are assessed. Resources for use in safety assessments can be pooled from the following sources:

- The Statement of Policy on FDA’s website.
- The Codex Alimentarius guidelines.
- Guidelines set out by the Organization for Economic Cooperation and Development (OECD).

We have certain flexibility about format and how the necessary information is presented to us.

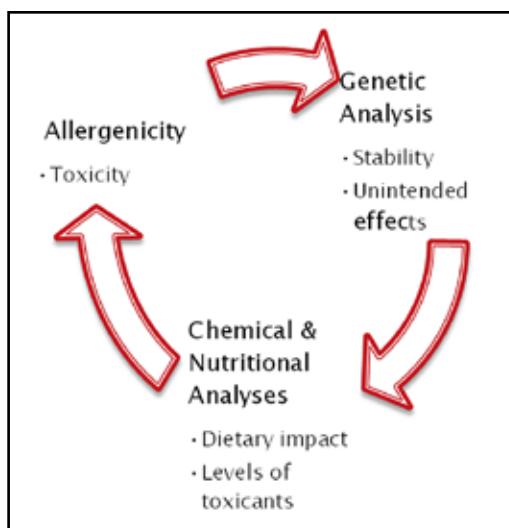


Figure 6. Safety assessment–2.

The safety of genetically engineered plants for food and feed is judged using a case-by-case approach. Generally, the genetically engineered plant is compared with a closely related conventionally developed plant, with the focus on new substances, *i.e.* toxicants, anti-nutrients, allergens and toxins. Bioinformatics are used to address the possibility that unintended new proteins are likely to be expressed, and if so, are they safe? The sequences of new proteins are compared with the sequences of known toxins, allergens and anti-nutrients.

For the molecular assessment, we require several pieces of information (Figure 7):

- Data showing which portions of the introduced DNA have been incorporated into the plant’s genome.
- Confirmation that there’s no vector backbone, with examination of the fidelity of insertion of the construct.

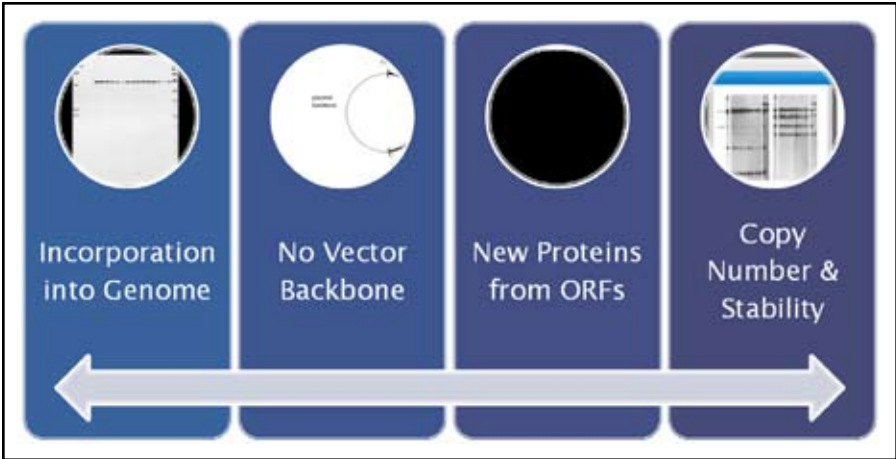


Figure 7. The molecular assessment.

- Evidence that no unintended proteins resulted from open reading frames. Ordinarily, that's based on bioinformatic analysis of the junction sequences of the insert.
- Information about copy number and stability, using genomic DNA blots or other appropriate technologies.

Next, compositional analyses are generally performed on field tests at multiple sites and usually over two growing seasons. The objective is to ensure that nutritional value is conserved, by comparing the new genetically engineered variety with a related control and/or a similar entity in the marketplace. Figure 8 illustrates the process for row crops. Key nutrients comprise proximates, *i.e.* fatty acids, fibers, amino acids, and vitamins and minerals. Again, we look at anti-nutrients, endogenous toxicants and endogenous allergens. For other types of crops, the analyses may be less comprehensive; in the case of fruit, the analyses usually comprise mostly fiber and sugar.

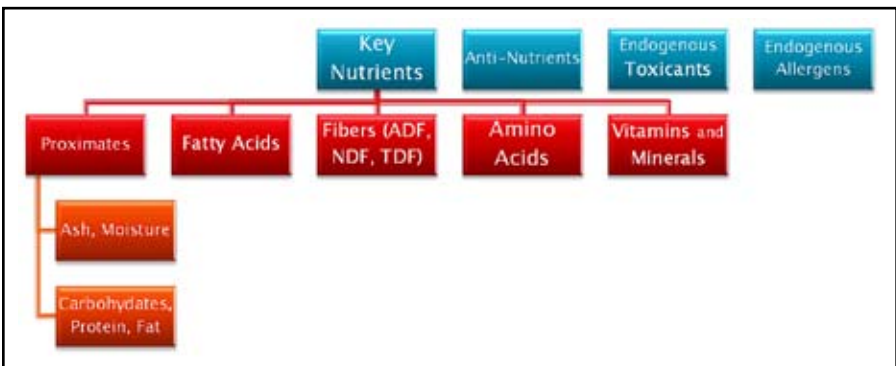


Figure 8. Compositional analyses.

## EXPERIENCE TO DATE

Corn, cotton, soybean, and canola have been the focus of most of our consultations. We have seen many varieties of these crops. Traits that we've covered can be classified as: herbicide tolerance, virus and insect resistance, altered oil composition, male sterility, delayed ripening, other altered composition, and agronomic changes (Figure 9).

As for the types of traits, we can group them in three basic categories (Figure 10). Both EPA and FDA have roles to play in assessing plant-incorporated protectants (PIPs).

Trait	Crops
Herbicide tolerance	alfalfa, canola, corn, cotton, soybean, sugar beet, creeping bentgrass, flax, rice
Virus Resistance	Squash, plum, papaya
Insect Resistance	corn, cotton, potato, soybean, tomato
Altered composition oils	Soybean, canola
Male Sterility	Corn, canola, radicchio
Delayed ripening	Tomato, cantaloupe
Altered composition	Corn (increased lysine) Canola (reduced phytate)
Agronomic changes	Corn

Figure 9. Traits and crops evaluated by FDA.

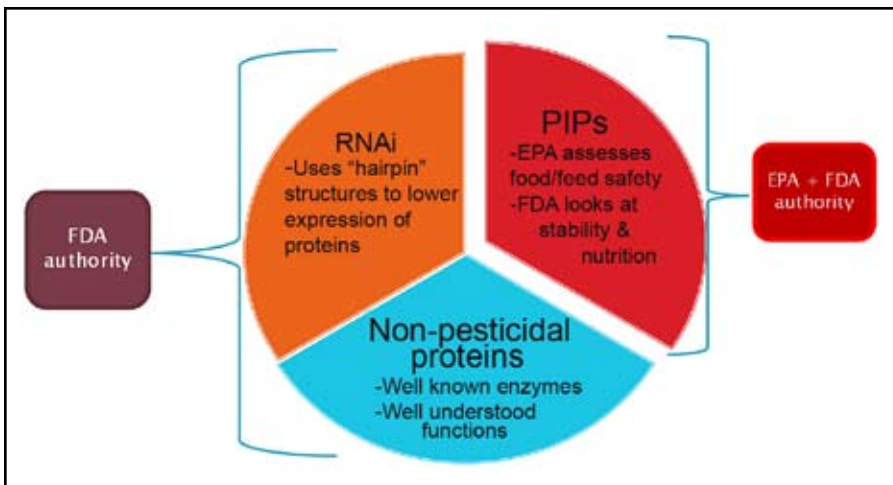


Figure 10. Types of traits.



Generally, FDA looks at stability and nutritional composition, whereas EPA looks at human and environmental safety via genomics and proteomics. For non-pesticidal proteins, FDA alone looks at food and feed safety. And FDA has had some submissions that utilize RNA inhibition.

**RISK COMMUNICATION**

Regarding risk communication, we try to be transparent to the degree that the law allows. Our inventory is available on the Internet (right side of Figure 11). If something is required of FDA that is not available on the Internet, a Freedom of Information Act request may be submitted. Also, we are happy to communicate directly via email, conventional mail, or by telephone. Figure 12 provides a list of resources; our main page is [www.fda.gov/geplantfoods](http://www.fda.gov/geplantfoods).

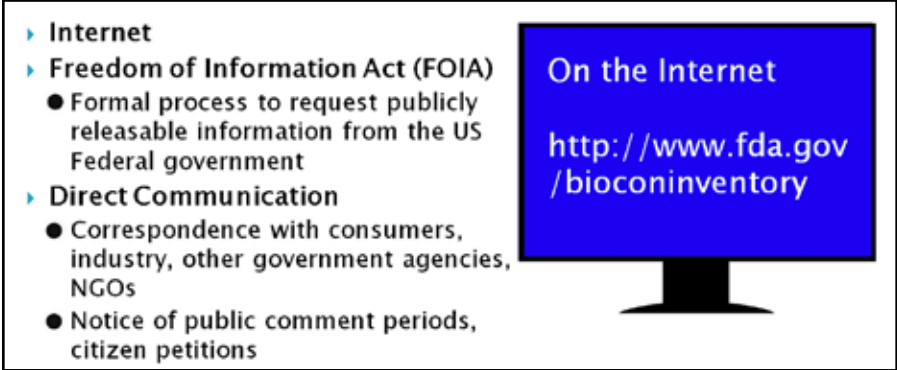


Figure 11. Transparency.

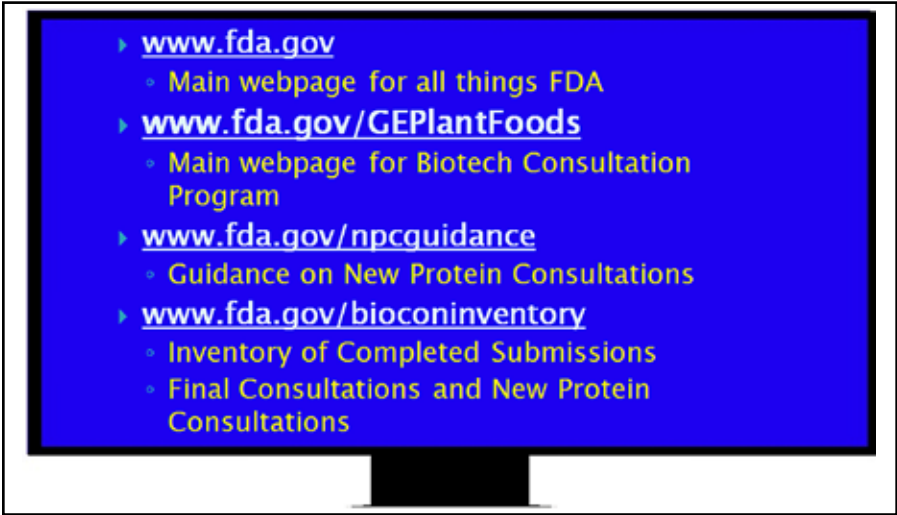


Figure 12. FDA's Internet resources.

## IN CONCLUSION

Our safety evaluations are based on the premise that genetically engineered plants are as safe as their traditionally bred counterparts. We encourage developers to engage with us prior to marketing, and we communicate with our sister government agencies and international groups to ensure that we're using both the best science and the best practices. We understand that, as science evolves, we will see new technologies and new traits; however, we expect that the policy that was developed in 1992 will remain sufficiently flexible and broad to accommodate them.



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**ROBERT MERKER** received his bachelor's degree in microbiology from the University of Illinois at Urbana-Champaign, and a PhD in microbiology from the University of California, Davis. After postdoctoral studies at the University of British Columbia and UC-Davis, he joined the Food and Drug Administration in 1991, where he did research on the outer surface of *Listeria monocytogenes*, acid tolerance in *Yersinia enterocolitica*, and the food safety of apple-cider production. In 2000, he became a consumer safety officer in the Office of Food Additive Safety.

He participated in the working group for the development of a *Codex Alimentarius* "Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms." He also has worked on a wide variety of biotechnology-related issues for FDA, and was a member of an interagency task team that has developed and maintains a joint Internet site for government information about regulation of the products of modern biotechnology.

Dr. Merker was selected as a supervisory consumer safety officer in the Division of Petition Review in the Office of Food Additive Safety in July 2007, and moved to the Division of Biotechnology and GRAS Notice Review in 2010, where he supervises several regulatory and environmental specialists. He oversees FDA's Consultations on Food from New Plant Varieties.