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**CFSAN/Office of Food Additive Safety  
Center for Veterinary Medicine  
June 2006**

## **Guidance for Industry**

# **Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use**

### ***GUIDANCE***

*Additional copies are available from:  
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Center for Food Safety and Applied Nutrition  
Center for Veterinary Medicine  
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<http://www.cfsan.fda.gov/guidance.html>

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## Guidance for Industry<sup>[1]</sup>

### Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

#### I. INTRODUCTION

This guidance is for developers of new plant varieties that are intended for food<sup>[2]</sup> use. The guidance describes procedures for the early food safety evaluation of new non-pesticidal<sup>[3]</sup> proteins<sup>[4]</sup> produced by such new plant varieties, including for example such proteins produced in bioengineered plants.<sup>[5]</sup>

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in agency guidances means that something is suggested or recommended, but not required.

#### II. BACKGROUND

Consistent with the Coordinated Framework for the Regulation of Biotechnology Products (51 FR 23302, June 26, 1986), the U.S. Office of Science and Technology Policy (OSTP) published a notice in the Federal Register of August 2, 2002 (67 FR 50578), in which it proposed federal actions to update field test requirements and to establish early voluntary food safety evaluations for new proteins produced by bioengineered plants ("the OSTP document"). Rapid developments in genomics are resulting in dramatic changes in the way new plant varieties are developed and commercialized. Scientific advances are expected to accelerate over the next decade, leading to the development and commercialization of a greater number and diversity of bioengineered crops. The U.S. Department of Agriculture/Animal and Plant Health Inspection Service (USDA/APHIS) oversees the field testing of new varieties of bioengineered plants and requires developers to follow procedures that minimize the chance of inadvertent introduction of material from these new varieties to agriculture, the environment, and the food supply. As the number and diversity of field tests for bioengineered plants increase however, the likelihood that cross-pollination due to pollen drift from field tests to commercial fields and commingling of seeds produced under field tests with commercial seeds or grain may also increase. This could result in the inadvertent, intermittent, low-level presence in the food supply of proteins

that have not been evaluated through FDA's voluntary consultation process for foods derived from new plant varieties (referred to as a "biotechnology consultation" in the case of bioengineered plants).<sup>[6]</sup> FDA is issuing this guidance document to address this possibility.

This guidance describes the procedure for early food safety evaluation of new proteins in new plant varieties that are under development for food use. In most cases, the proteins expected to become components of food, whether as a result of the use of traditional or modern biotechnology methods, will be the same or quite similar to proteins commonly found in food. FDA believes that any food safety concern related to such material entering the food supply would be limited to the potential that a new protein in food from the plant variety could cause an allergic reaction in susceptible people or could be a toxin in people or animals.

FDA first addressed the safety evaluation of new proteins in bioengineered plants in its 1992 Statement of Policy: Foods Derived from New Plant Varieties ("1992 policy;" 57 FR 22984, May 29, 1992).<sup>[7]</sup> The recommendations put forward in this guidance document are consistent with the scientific principles articulated in the 1992 policy for food safety evaluation of a new protein.

Since FDA first issued its 1992 policy, the agency has encouraged developers of new plant varieties, including those varieties developed through biotechnology, to consult with FDA early in the development process to discuss possible scientific and regulatory issues that might arise. This current guidance continues to foster early communication by encouraging developers to submit to FDA their evaluation of the food safety of their new protein. Such communication helps to ensure that any potential food safety issues regarding a new protein in a new plant variety are resolved early in development, prior to any inadvertent introduction into the food supply of material from that plant variety. Submission of an early food safety evaluation for a new protein is not meant to substitute for a biotechnology consultation with FDA about a food derived from a new bioengineered plant variety. If a developer decides to commercialize a new bioengineered plant variety, FDA expects that the developer will participate in the consultation process. A developer may use the information developed for the early food safety evaluation of a new protein in the biotechnology consultation process.

Consistent with confidentiality requirements, FDA will make submissions of early food safety evaluations for new proteins, and FDA's responses thereto, easily accessible to the public via the Internet. FDA believes this is consistent with the goal, as articulated in the OSTP document, of enhancing public confidence in the regulatory oversight of bioengineered plants.

### **III. SCOPE OF THE GUIDANCE**

FDA recommends that sponsors and developers of new plant varieties intended for food use consult with FDA about their evaluation of the food safety of any new proteins produced in these plants prior to the stage of development where the new proteins might inadvertently enter the food supply. Thus, the safety evaluation recommended by this guidance is termed an "early" food safety evaluation of new proteins. If a protein has been evaluated in an early food safety evaluation and no safety concerns are identified, we would not expect an additional early food safety evaluation to be submitted if the same protein is introduced into another plant species. Also, if a protein has previously been reviewed as part of a biotechnology consultation and there were no safety concerns identified, we would not expect you to submit an early food

safety evaluation for such a protein. This guidance does not apply to plant-incorporated protectants (PIPs), which are regulated by EPA.<sup>[8]</sup>

### **A. Terms I need to know for the purposes of this document**

- "You," "I," and "my" refer to the responsible person (developer or sponsor) who conducts the food safety evaluation and submits such information to FDA.
- "We," "us," and "our" refers to the FDA.
- Bioengineered plant (see footnote 5) means a recombinant-DNA plant. As used by Codex Alimentarius (see footnote 5), "recombinant-DNA plant" means a plant in which the genetic material has been changed through *in vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acids into cells or organelles.
- Food refers to food for man or other animals.
- New protein refers to any non-pesticidal protein produced in a new plant variety that is new to the plant species, or is a native protein that has been produced at a significantly elevated level, or is a native protein from a part of a plant that is not normally ingested, and will now be produced in a part of the plant that is normally ingested, and has not been the subject of a completed biotechnology consultation or a completed early food safety evaluation with FDA.
- A biotechnology notification file (BNF) is a file that FDA establishes and that contains information provided by a developer regarding the safety and nutritional assessment of a new bioengineered plant variety intended for food use.
- Plant-incorporated protectant (PIP) is a pesticidal substance that is intended to be produced and used in a living plant, or in the produce thereof, and the genetic material necessary for the production of such a pesticidal substance. It also includes any inert ingredient(s) contained in the plant, or produce thereof (40 CFR 174.3). EPA is responsible for the safety review and regulation of PIPs.
- Freedom of Information Act (FOIA; 5 U.S.C. 552) is a law that allows interested parties to request specific information and documents from a federal agency. FDA regulations regarding requests made under FOIA for data and information submitted to the agency are located at Title 21, part 20 of the Code of Federal Regulations.

### **B. What is the intent of this guidance?**

This guidance provides a scientific framework in which to evaluate the food safety of new proteins prior to the stage of development where the new proteins might inadvertently enter the food supply, and provides recommendations about communicating with us about your scientific evaluation.

As well, this document provides guidance about the format of a submission for the early food safety evaluation of a new protein.

### **C. General considerations**

### **1. When would I send a food safety evaluation for a new protein to FDA?**

We encourage you to submit to us your food safety evaluation of a new protein prior to the stage of development at which a new protein might inadvertently enter the food supply, for example, via pollen flow or commingling as you increase the size or extent of field testing.

### **2. How can I obtain information that will help me in preparing a food safety evaluation of my new protein?**

You can obtain current guidance regarding the preparation of your safety evaluation by writing to the Office of Food Additive Safety (OFAS) at the address listed previously or by looking on [OFAS's home page](http://www.cfsan.fda.gov/~lrd/foodadd.html) on the Internet (<http://www.cfsan.fda.gov/~lrd/foodadd.html>). You may also contact OFAS to schedule a meeting to discuss issues specific to your safety evaluation.

### **3. Does FDA recommend that I still participate in FDA's biotechnology consultation process, i.e., submit a BNF, even if I have communicated with FDA about the food safety of a new protein?**

Yes, we recommend that if you decide to commercialize your new plant variety that you participate in FDA's biotechnology consultation process even if you have submitted to us and completed the early food safety evaluation of the new protein in your bioengineered plant. You may use the information developed for your food safety evaluation of a new protein in the biotechnology consultation process. The biotechnology consultation process evaluates the full complement of food safety and regulatory issues based on the characteristics of the food, including potential unintended changes in the composition of the food.

## **IV. EARLY FOOD SAFETY EVALUATION OF NEW PROTEINS**

### **What are the important considerations in the early food safety evaluation of a new protein?**

You should consider whether the new protein is an allergen or a toxin.

While the 1992 policy addresses the full food safety evaluation of foods derived from new plant varieties, general considerations for conducting a food safety evaluation of a new protein, as well as flow charts diagramming specific questions relevant to such an evaluation, may also be found in the 1992 policy (see footnote 7).

We also encourage you to refer to the approach that is discussed in the Codex Alimentarius "Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants" (Codex Plant Guideline, see footnote 5) (CAC/GL 45-2003) Paragraphs 34-43 under *Expressed Substances (non-nucleic acid substances)* and the Codex Allergenicity Annex (see footnote 5).

## **V. COMMUNICATING WITH FDA**

## **A. My early food safety evaluation at FDA**

### **1. What happens when I send my safety evaluation to FDA?**

- We establish an administrative file for your safety evaluation.
- We acknowledge receipt of your safety evaluation.
- Our scientists will evaluate the information you submit.
- Our scientists may ask you questions about your safety evaluation.
- We will send a response to you about your safety evaluation.
- Your submission and our response will be made available to the public through our Internet site.

### **2. What information is included in the administrative file?**

- Your safety evaluation;
- Any correspondence between us;
- Any written materials that you provide; and,
- A memorandum of each meeting or significant phone call regarding the subject of your submission.

## **B. Communicating with FDA about my early food safety evaluation**

### **1. Do I need to have a meeting with FDA?**

It is not necessary to have a meeting with us to communicate about your early food safety evaluation of your new protein. If, however, you think a discussion with us would be useful to address issues that have arisen in your safety evaluation, we recommend that you request a meeting.

### **2. Where do I send my safety evaluation?**

Send your safety evaluation to OFAS at the address listed previously. CFSAN will coordinate FDA's evaluation of your request with CVM.

### **3. May I send my safety evaluation as an electronic file?**

Yes, you may send your safety evaluation as an electronic file plus one paper copy. Please contact OFAS before sending an electronic file to obtain specific guidance on electronic submission.<sup>[9]</sup>

### **4. If I choose to send a paper copy of my safety evaluation, how many copies do I send?**

A single copy of your safety evaluation is sufficient.

## **5. What if I am sending confidential commercial information?**

FDA will handle information submitted as part of a food safety evaluation of a new protein in accord with the requirements of the FOIA, other applicable statutes, and FDA's regulations at 21 CFR Part 20.

## **6. May I submit any data or other information, such as a reprint of a published scientific article, in a foreign language?**

If you submit any material in a foreign language, we request that you provide an accurate and complete English translation.

## **7. May I incorporate by reference data or other information that are already retained in FDA's files?**

If you previously submitted information to us, you may incorporate that information by reference.

If someone else previously submitted information to us, the procedure to be used to incorporate that information by reference into your submission depends on whether the information is publicly available (e.g., the information is in an electronic reading room or is otherwise available under FOIA). If the information is publicly available, you may incorporate that information by reference.

If the information is not publicly available, you may incorporate that information by reference only if the person who submitted the information authorizes you to do so in a signed statement and you include that signed statement in your safety evaluation.

If you choose to incorporate information by reference, you should describe the information in such a way that we can readily locate it.

## **8. May I withdraw my safety evaluation from FDA's consideration?**

At any time during our evaluation of your submission, you may request that we cease to evaluate it. Your request would not preclude you from sending a revised submission, nor prejudice a new submission about the same new protein at a later date. If you request that we cease to evaluate your submission, we will retain your submission in our files and classify your submission as "withdrawn".

## **C. Public disclosure of my early food safety evaluation**

### **What information about my submission and FDA's response will be available on the agency's Internet site?**

Consistent with confidentiality requirements, FDA will make the following information easily accessible to the public via the Internet:

1. The text of your submission; and,

2. The text of the response letter issued by us.

## **VI. FORMAT FOR SUBMISSION OF MY EARLY FOOD SAFETY EVALUATION**

We suggest that your submission consist of two parts. If any information requested in Part II does not apply, please explain why it does not apply.

### **Part I.**

Part I is your cover letter informing FDA that you are submitting your early evaluation of the food safety of a new protein. In your cover letter please include your name, position or title, address, telephone number, and electronic address.

### **Part II.**

Part II of your submission is where you explain your scientific evaluation of the food safety of your new protein by providing a synopsis of the safety data and information and your conclusions about potential food safety concerns if your protein inadvertently entered the food supply. These data and information should focus on whether the new protein is an allergen or a toxin. They should include:

1. The name, identity, and function of any new protein produced in the new plant variety;
2. Data and information as to whether the new protein has been safely consumed in foods;
3. A list of the identity (ies) and source(s) of the introduced genetic material;
4. A description of the purpose or intended technical effect of the new protein;
5. An assessment of the amino acid similarity between the new protein and known allergens and toxins;<sup>[10]</sup>
6. The overall stability of the protein, and the resistance of the protein to enzymatic degradation using appropriate in vitro assays;<sup>[11]</sup> and,
7. Any other pertinent information.

When data or information from 1-7 indicate that the new protein could potentially cause an allergic reaction in susceptible people or could be a toxin in people or animals, further evaluation is necessary. For other information that may be helpful in resolving these issues, you may refer to the Codex Plant Guideline, Paragraphs 34-43 under *Expressed Substances (non-nucleic acid substances)* and the Codex Allergenicity Annex for additional guidance. You may also consult with OFAS regarding these issues. When the source of the introduced genetic material is wheat, rye, barley, oats, or related cereal grains, the new protein may have the potential to elicit gluten-sensitive enteropathy in sensitive individuals. For additional guidance that may be helpful in resolving this issue, you may consult with OFAS.

## VII. FDA EVALUATION AND RESPONSE

### What will I receive from FDA and how long will it take?

1. Within 15 working days of receiving a submission, we plan to send you an acknowledgement letter that informs you of the date we received your submission.
  - (a) If your submission appears to include all of the recommended elements, we will add it to our inventory of early food safety evaluations of new proteins.
  - (b) If your submission does not appear to include all of the recommended elements, we will inform you of that fact and explain what we think should be included.
2. If FDA subsequently has questions about your submission, we may contact you to ask that you provide clarification or additional data as needed.
3. Within 120 days of receiving a submission that includes all of the recommended elements, we plan to send you a letter regarding our evaluation of your submission.

In general, FDA plans to respond as follows:

- (a) We are extending our evaluation of your submission by 120 days; or
- (b) We have completed our evaluation of your submission. Based upon this evaluation, and as discussed in this letter, the submission raises questions about the food safety of your new protein. Questions about the safety of your new protein should be resolved prior to engaging in any activity that might result in material from your plant inadvertently entering the food supply; or
- (c) We have completed our evaluation of your submission. Based upon this evaluation, we have no questions at this time regarding your view that the new protein raises no food safety concerns; or
- (d) We have received a letter from you stating that you have withdrawn your submission from consideration without prejudice to a future submission. Given your letter, we ceased to evaluate your submission on the date that we received your letter.

## VIII. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The time required to complete this information collection is estimated to average 20 hours per response, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to: Office of Food Additive Safety, Division of Biotechnology & GRAS Notice Review, HFS-255, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Parkway, College Park,

MD 20740.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0583 (expires 04/30/2009).

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[1] This guidance has been prepared by the Center for Food Safety and Applied Nutrition (CFSAN) in cooperation with the Center for Veterinary Medicine (CVM) at the U.S. Food and Drug Administration.

[2] In this document, food refers to both human food and animal feed, unless otherwise specifically stated.

[3] The Environmental Protection Agency (EPA) is responsible for evaluating the safety of pesticides, including plant-incorporated protectants. As such, these proteins are not subject to FDA review and are not the subject of this guidance.

[4] In this document we refer to such proteins as "new proteins."

[5] Bioengineered plants are also referred to as "biotechnology-derived plants" in the Office of Science and Technology Policy Federal Register notice (67 FR 50578, Aug. 2, 2002), and as "recombinant-DNA plants" by the Codex Alimentarius, in "Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants" (CAC/GL 45-2003), available at [ftp://ftp.fao.org/es/esn/food/guide\\_plants\\_en.pdf](ftp://ftp.fao.org/es/esn/food/guide_plants_en.pdf).

[6] Guidance on Consultation Procedures: Foods Derived from New Plant Varieties can be found at <http://www.cfsan.fda.gov/~lrd/consulpr.html>.

[7] The 1992 policy can be found at <http://www.cfsan.fda.gov/~acrobat/fr920529.pdf>.

[8] See the OSTP document for a discussion of proposed actions by EPA regarding EPA regulation of PIPs.

[9] You may also consult "Providing Regulatory Submissions in Electronic Format- General Considerations," available at <http://www.cfsan.fda.gov/dms/guidance.html>.

[10] For additional guidance on this issue, you may refer to the Codex Plant Guideline, Paragraph 38 under *Expressed Substances (non-nucleic acid substances)* and the Annex to the Codex Plant Guideline: Assessment of Possible Allergenicity (Codex Allergenicity Annex), Section 3.2 (see footnote 5).

[11] For additional guidance on this issue, you may refer to the Codex Plant Guideline, Paragraph 38 under *Expressed Substances (non-nucleic acid substances)* and the Codex Allergenicity Annex, Section 3.3.

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The above guidance document supercedes the [previous version](#) dated November 2004.

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