Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact the Center for Food Safety and Applied Nutrition (CFSAN) at 301-436-1200.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition
Center for Veterinary Medicine

November 2004

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition (CFSAN)
Center for Veterinary Medicine (CVM)

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Contains Nonbinding Recommendations

Draft — Not for Implementation

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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[2] use. The guidance describes procedures for the early food safety evaluation of new non-pesticidal[3] proteins[4] produced by such new plant varieties, focusing in particular on such proteins produced in bioengineered plants.[5]

[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.

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. As the number and diversity of field tests for bioengineered plants increase, the likelihood that cross-pollination due to pollen drift from field tests to commercial fields and commingling of seeds produced during 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).[6] 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. While this guidance is focused on new proteins in bioengineered plants, these procedures may, of course, be used for new proteins in non-bioengineered foods as well. FDA believes that any food safety concern related to such material

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

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).[7] 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 bioengineered plant variety are resolved early in development, prior to any possible 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. 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

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

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.[8]

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" and "us" 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 either new to the plant species, or is a native protein that has been produced at a significantly elevated level, 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.

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

- 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 voluntarily to the agency are located at Title 21, part 20 of the Code of Federal Regulations (21 CFR 20.111).

B. What is the intent of this guidance?

This guidance provides a scientific framework in which to evaluate the food safety of new proteins, and provides recommendations about communicating with us about your scientific evaluation. We recommend that you evaluate the food safety of new proteins early in the development process for your bioengineered plant.

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 time you have concerns that the new protein could 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 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 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 bioengineered foods, 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 2) (CAC/GL 45-2003) Paragraphs 34-43 under *Expressed Substances (non-nucleic acid substances)* and the Codex Allergenicity Annex available at ftp://ftp.fao.org/es/esn/food/guide_plants_en.pdf.

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.[9]

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.

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

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 data or other information that are already retained in FDA's files by referring to them?

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

If someone else previously submitted information to us, the procedure to be used to incorporate that information 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 referring FDA to it.

If the information is not publicly available, you may incorporate that information by referring FDA to it 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.

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 have two parts. If the information requested in a part 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 about the new protein. 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 the new protein(s) produced in the new plant variety;
2. Data and information as to whether this 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;[10]

6. The overall stability of the protein, and the resistance of the protein to enzymatic degradation using appropriate in vitro assays;[11] and,

7. Any other pertinent information.

When data or information from 1-7 indicate that the new protein is a toxin in humans or animals, or is an allergen in humans, 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, FDA will send 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.

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[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, available at ftp://ftp.fao.org/es/esn/food/guide_plants_en.pdf.

[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.

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. You may wish to discuss the identified issues with us 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.