



BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

January 24, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Draft Guidance for Industry: Recommendations for Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use (Draft Guidance); Docket No. 2004D-0369

To Whom It May Concern:

This letter is submitted by the Biotechnology Industry Organization (BIO), in response to the notice of availability for the Draft Guidance published by the Food and Drug Administration (FDA) in the Federal Register on November 24, 2004 (69 Fed. Reg. 68381). BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products, including biotechnology-derived crops.

BIO appreciates FDA's continuing commitment to ensuring the safety of the food supply through appropriate regulatory oversight of new plant varieties intended for food use. BIO supports FDA's intended expansion of the existing pre-market review process to provide for a science-based, early food safety evaluation of new non-pesticidal proteins produced by these new plant varieties and encourages FDA to implement the early safety evaluation process expeditiously.

The member companies of BIO are committed to the development of new biotechnology-derived plant varieties in compliance with appropriate confinement standards and good agricultural practices to minimize the potential for any inadvertent, intermittent, low-level presence in the food supply of proteins that have not yet completed the pre-market review process at FDA. Moreover, BIO and its member companies are committed to ensuring compliance with all applicable regulatory requirements issued by the Animal and Plant Health and Inspection Service (APHIS) and the Environmental Protection Agency (EPA), and regularly implement new educational and training programs to further that goal.

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Additional comments on the Draft Guidance and the collection of information provisions follow.

DRAFT GUIDANCE

General

BIO renews its support for the pre-market biotechnology notification (PBN) rule proposed by FDA on January 18, 2001 (66 Fed. Reg. 4706), and urges FDA to finalize that rule at the earliest possible time. BIO strongly endorses a mandatory pre-market notification process that will ensure review by the FDA of all food and feed products produced using biotechnology and enhance consumer access to product information and agency determinations. FDA's proposed PBN rule would strengthen the current consultation process that has worked well since 1992. BIO member companies have consulted with FDA on all products that are on the market today and fully support a rigorous FDA review process.

The PBN Rule would formalize a procedure for the submission and review of pre-market notifications for biotechnology-derived foods, enhance the transparency of the review process and address FDA's enforcement authority as it applies to biotechnology-derived food that might be marketed without satisfactory completion of the PBN process. Prompt action to finalize the PBN Rule is needed to further strengthen U.S. government policy related to biotechnology, reassure the public, food and commodity groups, agricultural interests and food export markets of the safety of all biotechnology-derived foods grown in the U.S., and to ensure the safety of the domestic food supply, particularly with respect to future imports from developing nations.

For new, non-pesticidal proteins produced by crops intended for food or feed use, food safety evaluations should be conducted at an earlier stage in the development process than the current pre-market consultation or the proposed PBN process. BIO strongly encourages FDA to finalize and implement the Guidance immediately as an important first step in achieving this objective. FDA should then take the necessary administrative actions to make the early food safety evaluation a part of the FDA's pre-market review process, with careful attention given to the stage at which early evaluations would be appropriate. As indicated in the Draft Guidance, submissions should be made to FDA prior to the time that the new protein might be found at low, intermittent levels in the food supply as the size and extent of field testing increase.

Science-based Review

BIO applauds FDA's commitment to a science-based review process consistent with any potential risk that might be posed by food derived from new plant varieties. In terms of

the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use, we support the focus on the safety of new proteins.

This is particularly appropriate at the early stages of product development where the low-level intermittent exposure that might occur would not warrant evaluation of any potential, unintended compositional changes. Any such changes would of course be reviewed as part of the FDA's pre-market consultation process for new plant varieties. Furthermore, BIO supports an early safety evaluation consistent with the toxicity and allergenicity assessment of any new protein currently conducted as part of the FDA's consultation process. This assessment focuses on the protein conferring the trait of interest and relies on the science-based decision-tree approach under the agency's 1992 Statement of Policy: Foods Derived from New Plant Varieties (57 Fed. Reg. 22984, May 29, 1992).

BIO encourages FDA to include in the Guidance a clear reference to the underlying scientific principles relied upon by FDA, APHIS, EPA and the Office of Science and Technology Policy (OSTP) in developing the federal government's policy for updating field test requirements for biotechnology-derived plants and establishing early food safety assessments for new proteins produced by such plants (67 Fed. Reg. 50578, Aug. 2, 2002). In particular, OSTP cited the following three principles:

- The level of confinement under which a field test is conducted should be consistent with the level of environmental, human, and animal health risk associated with the introduced protein and trait;
- If a trait or protein presents an unacceptable risk or the risks cannot be determined adequately, field test confinement requirements would be rigorous to restrict out-crossing and commingling of seed and the occurrence at any level of biotechnology-derived genes and gene products from these field tests would be prohibited in commercial seed, commodities, and processed food and feed; and
- Even if a trait or protein does not present an unacceptable risk to the environment or public health, field test requirements should still minimize the occurrence of out-crossing and commingling of seed from these field tests, but intermittent, low levels of biotechnology-derived genes and gene products from such field tests could be found acceptable based on data and information indicating the newly introduced traits and proteins meet the applicable regulatory standards.

Imports

In keeping with the scope of the Federal Food, Drug, and Cosmetic Act (FFDCA), the 1992 FDA Statement of Policy, and the 2002 OSTP Policy, the Guidance should state

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unequivocally that it applies to new plant varieties being developed in nations that export food or feed commodities to the United States. This is particularly important given the increasing volume and diversity of research being conducted in biotechnology-derived food and feed crops throughout the world.¹

Proteins Subject to Early Safety Evaluation

The Draft Guidance and the 2002 OSTP Policy are clearly and appropriately focused on the potential low-level presence of new proteins that are under development and have not yet been evaluated through FDA's pre-market consultation process. To the extent that there is any exposure at all, the expectation of low-level exposure is based on the negligible levels of biotechnology-derived material that might occur in food or feed at the field test stage due to the strict confinement of all research trials, the minimal potential for movement of material from the test site, and the extensive dilution factor associated with any such presence.

BIO agrees with the position taken in the 2002 OSTP Policy that not every biotechnology-derived protein will require a unique early food safety evaluation. As FDA indicated at that time, for this kind of low-level exposure, the agency would not expect a need for (a) submissions for proteins moved within the same species, as such movement would not raise new toxicity or allergenicity issues for the food, or (b) evaluations to include potential unintended compositional changes in food that would be evaluated during the consultation process prior to any marketing of food or feed. The Draft Guidance appears to be at odds with the foregoing principles by defining a "new protein" to include a native protein that has been produced at "a significantly elevated level." This departure does not appear to be scientifically justified and would also unnecessarily increase the burden associated with the early evaluation process.

BIO recommends that the Guidance adhere to the principles as stated by FDA in 2002 and supports the adoption by FDA of science-based exemptions that identify categories of proteins for which individual reviews will not be required based on prior food safety evaluations, a history of safe use or a lack of new exposure. Proteins or proteins present in crops that have previously been cleared for food and feed use in the United States, have a known history of safe use, or are closely related to a protein that meets these criteria – "familiar" proteins – should be exempted from the early food safety assessment process as intermittent, low levels of these proteins in the food or feed supply would not raise safety concerns. This process should be ongoing, allowing for addition of other familiar proteins to the exemption list and communication once a protein has been placed on the list.

¹ An excellent source of information on this topic can be found on the web site of the International Service for the Acquisition of Agri-biotech Applications (www.isaaa.org).

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Codex

BIO endorses FDA's use of the Codex Guidelines. These guidelines represent the internationally recognized standard for the conduct of food safety assessments for foods derived from biotechnology-derived plants and are consistent with the regulatory guidelines and decision trees that FDA articulated in its 1992 policy.

Transparency

BIO supports FDA's plan to provide for public access to information concerning the early food safety evaluation process consistent with confidentiality requirements of federal law. In making submissions for early food safety evaluations, and FDA's responses thereto, easily accessible to the public via the Internet, FDA should exercise care in order to ensure that the early stage of development of the plants and proteins reviewed is clearly and accurately characterized. Recognizing the early stage of product development at which early safety evaluations will typically occur, FDA's Guidance should clearly indicate to developers the point at which any information concerning the evaluation will become public. It would also be valuable for FDA to coordinate with EPA to maintain a joint list of proteins (non-pesticidal and pesticidal) that have completed appropriate food safety review(s) in order to enhance the ease of public access to this information.

FDA Review Period

BIO believes the proposed 120-day evaluation period is too long and recommends that FDA consider an initial evaluation period of 90 days.

Flexibility

BIO agrees with FDA that alternative approaches to meeting the intent of the Guidance should be permitted assuming the alternative satisfies the applicable requirements. Flexibility is particularly appropriate given the rapid rate of scientific advances and the evolution in methodologies.

INFORMATION COLLECTION REQUEST (ICR)

General

BIO considers the proposed collection of information to be necessary for the proper performance of FDA's functions under the FFDCA, the 1992 FDA Statement of Policy and the Coordinated Framework for Regulation of Biotechnology (51 Fed. Reg. 23302, June 26, 1986). The information to be collected will have considerable practical utility to

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FDA in conducting its review of early food safety evaluations for new non-pesticidal proteins produced by new plant varieties intended for food use.

The burden associated with the collection of information, while not insignificant, should be manageable as a result of (a) FDA's approach of expecting one evaluation per new protein and adoption of science-based exemptions that identify categories of proteins for which individual reviews will not be required based on prior food safety evaluations, a history of safe use or a lack of new exposure, and (b) FDA's focus on those proteins involved in field tests of increased size and extent.

Additional comments bearing on minimization of the burden as well as enhancing the quality, utility and clarity of the information collected are provided below.

Pesticidal Proteins

The scope of the proposed collection of information is appropriately limited to non-pesticidal proteins. Pesticidal proteins are regulated by EPA as plant-incorporated protectants under the food safety provisions of Section 408 of the FFDCA (21 U.S.C. 346a), and under the permit and registration requirements of the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136 et seq.). Conducting an early food safety evaluation at FDA would duplicate the food safety review made by EPA and create an unnecessary source of confusion and delay in the regulatory and product development processes. A discussion of EPA's proposed actions regarding pesticidal proteins is included in the 2002 OSTP document (67 Fed. Reg. 50579-80).

Original Data

There are several publicly available protein databases that can be utilized for toxin and allergen searches (e.g., <http://www.bioscience.org/urllists/proserch.htm>; Swiss-Prot, <http://www.ebi.ac.uk/swissprot/>). For databases specific for allergens, the FARRP allergen database (University of Nebraska) and the European Informall allergen database (<http://www.allergenonline.com/>; <http://www.informall.eu.com/database.htm>) may be utilized.

Evaluation of Potential Allergenicity

FDA should clarify that a weight of the evidence approach is applied to assess the potential allergenicity of new proteins. In addition, the review of available information on the new protein's susceptibility to enzymatic degradation is carried out in context, where the intent is to address whether the potential for the food produced from a biotechnology-derived plant to induce an allergic response has been altered by the genetic modification. These principles are fully in keeping with the manner in which potential

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allergenicity of new proteins has been reviewed by FDA under the existing pre-market consultation process.

As stated above, alternative approaches to meet the intent of the early food safety evaluation should be permitted if an alternative satisfies the applicable requirements. Currently, resistance to pepsin digestibility is generally used in the assessment of potential allergenicity. The Codex Alimentarius "Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants," to which FDA encourages industry to refer, clearly states in the Annex on Assessment of Possible Allergenicity, that "[a]lthough a pepsin resistance protocol is strongly recommended, it is recognized that other enzyme susceptibility protocols exist. Alternative protocols may be used where adequate justification is provided." This flexibility is required as our understanding of appropriate approaches expands and alternative protocols are developed in the assessment of allergenicity. With the development of protocols, it will become important to develop consistent approaches and standardized protocols for allergenicity assessment, such as those recently published under the auspices of the International Life Sciences Institute/Health and Environmental Sciences Institute² and Dow AgroSciences LLC.³

We appreciate the opportunity to provide comments on the Draft Guidance and look forward to working with FDA as it moves to fully implement the early food safety evaluation process.

Sincerely,



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² Thomas, K., Aalbers, M., Bannon, G.A., Bartels, M., Dearman, R.J., Esdaile, D.J., Fu, T.J., Glatt, C.M., Hadfield, N., Hatzos, C., Hefle, S.L., Heylings, J.R., Goodman, R.E., Henry, B., Hérouet, C., Holsapple, M., Ladics, G.S., Landry, T.D., MacIntosh, S.C., Rice, E.A., Privalle, L.S., Steiner, H.Y., Teshima, R., Thomas, K., van Ree, R., Woolhiser, M., Zawodny, J. "A multi-laboratory evaluation of a common in vitro pepsin digestion assay protocol used in assessing the safety of novel proteins." *Reg. Tox. Pharma.*, 39:87-98 (2004).

³ Herman, R.A., Korjagin, V.A., Schafer, B.W. "Quantitative measurement of protein digestion in simulated gastric fluid." *Reg. Tox. Pharma.*, _____ (2005).