



February 7, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket No. 02D-0324

To whom it may concern:

The following comments are submitted by the Biotechnology Industry Organization (BIO), in response to the draft “Guidance for Industry: Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals,” (the Draft Guidance).¹ BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states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 intended for uses other than food or feed. BIO and its member companies involved in the development and commercialization of biotechnology-derived plants and plant products are committed to ensuring the safety of these products at all stages of development and production.

Draft Guidance

BIO fully supports the efforts of the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA) to develop the Draft Guidance. Strong regulatory oversight by these agencies (together with the U.S. Environmental Protection Agency (EPA), where appropriate) has been a key element of the Coordinated Framework for the Regulation of Biotechnology (Coordinated Framework) since its inception in 1986. Regulatory policies and decisions must continue to be based on sound science, while ensuring that biotechnology-derived products are being held to the same high standards of health and environmental safety as all other regulated products.

¹ See 67 Fed. Reg. 57828 (Sept. 12, 2002).

Maintaining this approach will allow the benefits of plant-made pharmaceuticals (PMPs) to be made available to those in need, while facilitating the free flow of U.S. agricultural products in international trade.

The Coordinated Framework anticipated that specific regulations and guidance would be needed in light of scientific advances and product development. In the years since 1986, the agencies have relied on their existing statutory authorities to issue appropriate rules, policies and guidance. The increase in the number and diversity of biotechnology-derived crops under development, including PMPs, suggests that this is an appropriate time to enhance existing guidance, standards and procedures for the production of these products.

The inter-agency cooperation and communication envisioned by the Coordinated Framework is well demonstrated in the Draft Guidance, which recognizes the authority of the various agencies sharing authorship of the document over the various aspects of production of these products. While this joint Draft Guidance is an appropriate regulatory vehicle by which to address the proper production of these products, it should in no way be seen as the ultimate, or only, regulation of PMPs. USDA has stated its intent to increase the stringency with which it regulates PMPs. BIO and its members support this action, and express their desire to work with USDA's Animal and Plant Health Inspection Service (APHIS) and Biotechnology Regulatory Services (BRS) to further improve a system that has already proven itself protective of the environment and the food supply.

The Draft Guidance provides helpful guidance regarding issues related to the safety, purity and efficacy of the "regulated products," defined in the Draft Guidance as "FDA- or CVB-regulated intermediates, and biological products, vaccines, and drugs, intended for human or animal use and/or animal feed." BIO and its member companies believe that the voluntary nature offered by the guidance document structure is customary and well understood in the pharmaceutical community. It is an appropriate means of outlining important scientific questions and information that should be addressed early on during the mandatory investigation and approval process for drugs and biologics subject to FDA and USDA's respective drug and biologic regulatory approval processes. It is through these approvals that the safety, purity and efficacy of new drugs and biologics are assessed, and the guidance format is appropriate to instruct applicants how best to meet specific criteria in their approval applications.

The Draft Guidance also addresses environmental and confinement measures related to the production of these regulated products in plants. These measures relate primarily to potential environmental and human health effects. While it is important that these issues be considered by any potential manufacturer of regulated products, BIO and its member companies believe that these environmental and confinement measures should also be addressed in a separate regulatory forum. A separate regulatory statement by USDA, developed in coordination with other agencies as appropriate, would provide clarity not only for the production of these regulated products, but for other crops produced through

biotechnology, but which are intended for uses other than food or feed, such as plant-made industrial products (PMIPs).

This position is consistent with the recent proposal for USDA's amendment of its regulations governing products of biotechnology.² That policy proposal, published by the Office of Science and Technology Policy (OSTP), outlines steps that USDA has taken, and intends to take, with regard to the regulation of field-testing and commercial movement of plants derived from biotechnology. These steps are part of an overall updating of 7 CFR Part 340, which will incorporate USDA's new authorities under the Plant Protection Act (PPA),³ and will consider recommendations made to USDA in the National Research Council (February 2002) report, "Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation."⁴ In the context of the upcoming revisions to 7 CFR Part 340, a number of the recommendations discussed in the Draft Guidance should be mandated in those future USDA regulations. Others may be set forth as permit conditions or in a separate guidance document. BIO supports rigorous enforcement of all regulatory requirements and permit conditions.

Accordingly, BIO's comments on the Draft Guidance fall into two general categories. BIO raises specific questions, comments and requests for clarification raised by the Draft Guidance in a separate "Attachment 1" to this letter. These comments relate primarily, but not exclusively, to issues relating to the safety, purity and efficacy of the biological products being produced by PMP crops. Below, BIO provides broader suggestions for future regulation of these, and similar, crops by USDA under the PPA, building on the recommendations contained in the Draft Guidance.

Recommendations for USDA Oversight Under the Plant Protection Act

1. Regulation of Industrial Crops

Crops that are developed through biotechnology for industrial use cover a broad spectrum of products; some of which may be intended for food or feed use, others that are clearly intended not to be used for food or feed. For the purposes of these comments, the term plant-made industrial products (PMIPs) refers only to those products intended not to be used for food or feed. The Plant Protection Act grants USDA the authority to regulate the movement of both PMPs and PMIPs in order to protect the environment, human and livestock safety, and the agricultural economy.⁵ Pursuant to this authority, USDA should require that PMIPs be grown, like pharmaceuticals, only under permit, both during field testing and upon commercialization. Deregulation of these products would not be appropriate at the present time.

² 67 Fed. Reg. 50578, 50580 (Aug. 2, 2002) (announcing "Proposed Federal Actions to Update Field Test Requirements for Biotechnology Derived Plants and to Establish Early Food Safety Assessments for New Proteins Produced by Such Plants").

³ 7 U.S.C. § 7701 *et seq.*

⁴ 67 Fed. Reg. at 50580.

⁵ 7 U.S.C. § 7701 *et seq.*

2. Food/Feed Adulteration Concerns

Throughout the Draft Guidance, particularly in Section III, “Environmental Considerations,” recommendations are made regarding the need to “control the spread of the bioengineered pharmaceutical plants and to keep them from entering the food or feed supply.” (Draft Guidance, ll. 416-418.) As discussed above, BIO believes that many of these recommendations should also be addressed separately by USDA, and applied to both PMPs and PMIPs.

Detailed scientific and regulatory analyses suggest that PMPs and PMIPs can be safely planted, grown and harvested in an agricultural region where all of the appropriate production and confinement handling practices are implemented. However, one measure specifically referenced in the Draft Guidance to protect against the unintentional adulteration of the food/feed supply is the possibility of growing PMPs derived from outcrossing food crops in regions of the country where little or none of the crop’s food/feed counterparts are grown. (See Draft Guidance ll. 484-490.) BIO appreciates USDA’s interest in identifying alternative means for isolation of regulated articles that are derived from outcrossing food and feed crops, but which are intended not to be in food or feed. BIO members will follow the protective measures prescribed by USDA, including physical, temporal and biological isolation, as well as appropriate spatial isolation and acreage limitations.

3. Performance Verified Testing Procedures

BIO supports action by USDA to require applicants for PMP and PMIP permits to provide regulatory authorities with performance verified testing methodologies to detect both the presence of the target gene and the protein product in the raw agricultural commodity.⁶ However, with regard to the possibility that the mere presence of the target gene could render food adulterated under the Federal Food, Drug, and Cosmetic Act, BIO and its members strongly endorse the position repeatedly cited by FDA regarding the ubiquitous nature and safety of DNA.⁷ Testing for the presence of the target gene could

⁶ See, e.g., GIPSA Directive 9181.2, “Performance Verification of Rapid Tests for the Detection of Biotechnology Events.”

⁷ See, e.g., “Statement of Policy: Foods Derived from New Plant Varieties,” 57 Fed. Reg. 22,984, 22,990 (May 29, 1992) (“Nucleic acids are present in the cells of every living organism, including every plant and animal used for food by humans or animals, and do not raise a safety concern as a component of food.”); proposed “Premarket Notice Concerning Bioengineered Foods,” 66 Fed. Reg. 4706, 4709 (Jan. 18, 2001) (“The agency reiterates its view, as stated in the 1992 policy (57 FR 22990), that transferred genetic material can be presumed to be GRAS.”)

be an initial step in a validated testing protocol, but the mere presence of the target gene alone should not be sufficient to render food or feed adulterated.

4. National Environmental Policy Act

BIO and its members support PMP and PMIP permit requirements that address the potential environmental impacts associated with the scale of production, protein of interest and crop at issue. These could be structured to address many of the issues analyzed under a National Environmental Policy Act (NEPA) assessment. However, following well-established regulatory criteria, a NEPA environmental assessment would likely be appropriate prior to permitting of production at commercial scale of a PMP or PMIP grown in open fields.

5. Standard Operating Procedures

BIO and its members support PMP and PMIP permit conditions requiring the implementation of stringent Standard Operating Procedures (SOPs), focused on critical production activities (e.g., planting, harvest, etc.) consistent with a Hazard Analysis and Critical Control Point (HACCP) approach. Such confinement measures and SOPs should be appropriate to each stage of product development. BIO members have previously committed to submit detailed confinement plans and SOPs with all of their permit applications. We strongly encourage the agency to treat these plans and procedures as permit conditions, subject to audit and inspection.

6. Site Security

The Draft Guidance discusses the potential use of both distinguishing phenotypic characteristics (*See* Draft Guidance at ll. 481-82) and perimeter fencing (*id.* at ll. 533-34). BIO members feel that these measures provide minimal protection to the food/feed supply or the environment, and may unduly compromise site security of these fields. Such requirements should not be mandated in any way for these crops, although an individual company may choose to implement them.

7. Dedicated Equipment

BIO members agree that dedicated equipment is both appropriate and necessary for planting and harvesting to help ensure that genetic material from PMPs and PMIPs do not enter the food/feed supply. However, it should be clarified that the term “dedicated equipment” is meant to exclude the use of this equipment for the planting or harvesting of crops intended for food/feed use. Like other manufacturing equipment used for the production of regulated products, appropriate cleaning procedures may be used to ensure purity of the regulated product, and each regulated product should not require “individually dedicated” equipment. Similarly, while the immediate transportation containers should be dedicated and contained, the larger transportation equipment (e.g., a cargo plane containing sealed boxes) need not be dedicated.

8. Dedicated Land

BIO and its members support the use of dedicated land in the field-testing and production of PMPs and PMIPs to help ensure that recombinant proteins from these crops do not enter the food or feed supply. Dedicated land for the testing or production of PMPs or PMIPS must have a USDA-approved plant-back process for subsequent growing seasons. This process may entail physical, chemical or genetic controls, restricted crop rotations or the requirement for the land to lie fallow for a minimum of one growing season (or longer if scientifically supported) before it can be used in the production of crops intended for use as food or feed. If different PMPs or PMIPs are to be grown on the same land in subsequent years, appropriate quality assurance measures should be taken to control the quality of the raw agricultural material and the regulated product.

9. Contract Growers

BIO and its members support permit conditions requiring PMPs and PMIPs to be grown only by direct employees of the technology provider, or under written contract between the technology provider and the grower. A written contract provides added assurance that permit conditions and SOPs will be followed and appropriate training will be in place. Written contracts also facilitate USDA oversight.

BIO and its members very much appreciate the opportunity to comment on the Draft Guidance, and look forward to working with all the author agencies to find ways of fulfilling the promise of this technology, while protecting the health and safety of the public and the environment.

Sincerely,

A handwritten signature in cursive script that reads "Michael J. Phillips".

Michael J. Phillips, Ph.D.
Executive Director
Food and Agriculture

Enclosure

Docket No. 02D-0324

Specific comments submitted by the Biotechnology Industry Organization (BIO), in response to the draft “Guidance for Industry: Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals,” (the Draft Guidance):

1. **IA.** The scope of the Draft Guidance should be clarified to stipulate that it applies not only to private companies, but also to university, private and government activities in this area, as well.
2. **IB.** BIO would like to see plant residue waste material issues specifically addressed in this section, in the context of continued management by USDA.
3. **IIA.** BIO suggests that, in the interests of clarification, line 224/225 be changed from “non-food (or non-feed)” to: “non-food/feed”.
4. **IIC2.** BIO encourages the addition of specific references on characterization of DNA such as International Conference on Harmonization (ICH), FDA guidance and points-to-consider, and comments regarding harmonization with EU guidance documents.
5. **IIC3.** BIO supports the requirement, rather than recommendation, of a suitable transformant, as described in ll. 305-307.
6. **IIC3.** This section does not fully address those issues impacting the use of clonal propagation as a stable transformation system. BIO suggests that this section be expanded to include comments on clonal propagation.
7. **IIC4.** BIO recommends that this section be expanded to directly address transient system stability, a sampling system to detect genetic drift after transfection, and a requirement to establish limits of genetic drift.
8. **IIC5.** BIO suggests that this section be expanded to include an expanded definition of how the terms, “Master Seed Bank” (MSB) and “Working Seed Bank” (WSB) are defined, relative to standard agronomic practices, and to clonal propagation practices of plants. This section should also define and detail the validation of a MSB and WSB plant host, or provide reference to applicable existing guidance documents that provide such information.
9. **IIC5.** BIO recommends that lines 373 – 375 be changed along the lines of the following: “Regardless of whether a transient-transfection system or stable transfection system is used, you should prepare a banking system that will

ensure consistent lot-to-lot growth of the plant and expression of the regulated product."

10. **IIIC6.** BIO would appreciate clarification of the request for information regarding tissue distribution. If this information is requested for issues of food safety, it may be better addressed under USDA Plant Protection Act oversight.
11. **IIIB.** In addition to the comments set forth on NEPA matters in the body of this letter, BIO also suggests that this section contain general language describing those activities that would trigger the requirement of an Environmental Assessment, e.g., from FDA CBER Guidance for Industry, Environmental Assessment of Human and Biologics Applications, CMC 6.
12. **IIIC1.** In lines 487-488, BIO recommends that the sentence be modified, so as to read as follows: "... or by use of genetic controls that restrict the conditions under which..."
13. **IIIC1.** In lines 492-503, BIO recommends that a statement be included requiring a USDA test certification and standardization program.
14. **IIIC1.** In lines 492-503, BIO recommends that language be included specifically noting the use of SOPs, batch records, and good agricultural practices as control measures to restrict unintended exposure of a regulated product.
15. **IIIC1.** In lines 492-503, BIO recommends inserting a sentence along the lines of the following: "The use of dedicated seed and plant material storage facilities that are external to commodity grain channels will be a requirement for obtaining a field release permit from USDA".
16. **IIIC1.** In lines 492-503, BIO recommends that language be included specifically emphasizing that these processes are subject to USDA inspection, especially during critical agronomic phases.
17. **IIIC1.** This section should state that the availability of Contingency Plans for the Confinement Measures will be a requirement for obtaining a field release permit from USDA under the PPA. Those Plans should address response and mitigation procedures, and a monitoring plan to confirm the effectiveness of field confinement procedures.
18. **IIIC3.** In lines 533-534, the statement regarding the use of perimeter fencing should be clarified or omitted. The use of fencing may be in conflict with security measures based on concealment. The use of fencing would also be ineffective with regard to birds, insects, and small mammals. Any issue

regarding fencing should be based on specific product review regarding toxicity, environmental impact, etc. and specific issues should dictate the level of containment, which may or may not include fencing.

19. **IIIC5.** Lines 559 to 562 should state that raw source plant material should not be stored in equipment also used for the storage of food or feed products or ingredients. Also, BIO recommends that line 559 be clarified as follows: “Raw source plant material should not be processed in equipment that is also used for the production of food or feed, without prior consultation with USDA/APHIS/BRS or FDA regarding appropriate cleaning procedures for multi-purpose equipment that comes into direct contact with source plant material.”
20. **IIIC6.** Lines 565-568 should be clarified to state that any “regulated product” present in in-process wastes be rendered non-viable, rather than “inactivated.” There are many instances where some in-process wastes, such as column wash solutions, do not go through a true inactivation process prior to disposal.
21. **IVB.** This section should include some reference to a validated testing system that addresses consistent levels of target product in the plant host.
22. **IVD3.** In line 732, the sentence recommending the use of dedicated equipment should be changed to “PMP or PMIP harvesting equipment will not be used for harvesting products intended for food or feed use. This is a requirement for obtaining a field release permit from USDA under the PPA”, and the last sentence, line 746, “If the equipment is not dedicated to harvesting only the source material, other uses should be documented,” should be deleted.
23. **IVD3.** In this section, the term “dedicated equipment” should be defined as equipment not used for products intended for food or feed. Equipment can be used for different PMP and/or PMIP protein entities if there is a validated cleaning protocol and changeover protocol utilized prior to use. Equipment utilized for the production of PMPs and/or PMIPs should undergo an on-site, audited decommissioning process either at the end of its useful life cycle, or prior to any food or feed production use.
24. **IVD4.** In lines 751-759, a statement should be added along the lines of the following: “transportation and storage equipment that comes into direct contact with PMP or PMIP plant source material should not be used for transportation or storage of products intended for food or feed. For clarity, a bulk hopper trailer that has direct contact with PMP or PMIP plant source material should never be used for products intended for food or feed. However, a dry van used to transport one ton totes containing PMP or PMIP plant source material is not restricted in its future use.”

25. **IVD4.** In lines 757-759, BIO suggests that the sentence recommending “a label that clearly indicates that the material is not to be used for food or feed” should be changed to state that use of such a label will be a requirement for obtaining a field release permit from USDA under the PPA.
26. **IVD5.** This section should be expanded to address container requirements for handling and processing PMP and PMIP plants to ensure that dedicated containers are utilized.
27. **IVD6.** This section includes references for Extraction (6) and Aseptic Processing (7). Although purification processes will be similar to those already employed for biotechnologically derived proteins, transgenic plants used to produce pharmaceuticals will have unique purification requirements. We recommend that a section addressing purification be added after section IV.D.6. This section should include requirements for validated procedures for the removal of normal process-derived impurities such as pesticides, herbicide, fungicide and fertilizer residues.
28. **IVF.** Lines 891-893 should be clarified with regard to ICH stability procedures.
28. **VB1.** BIO recommends that the wording of line 940 be changed from “may be appropriate” to “shall be performed.”