CSPI Center for Science in the Public Interest

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February 6, 2003

By Regular and Electronic Mail
Dockets Management Branch [HFA-305]
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Comments on Draft "Guidance for Industry: Drugs, Biologics, and Medical Devices Derived From Bioengineered Plants for Use in Humans and Animals" [Docket No. 02D-0324].

The Center for Science in the Public Interest ("CSPI")[1] hereby submits comments to the Food and Drug Administration ("FDA") on its draft guidance announced in the Federal Register on September 12, 2002 (67 FR 57828) (hereinafter referred to as "Draft Guidance") addressing the regulatory process surrounding the commercial production of human or animal drugs or biologics in a plant. The use of genetic engineering of plants to product pharmaceuticals ("pharming") has the potential to provide tremendous consumer benefits, but if misused, also has the potential to harm consumers and the environment. Thus, a strong and transparent regulatory process with detailed guidance is essential if our society is to reap the benefits from safe commercial applications of pharming.

Although guidance setting forth the government's expectations for safety information needed for regulatory approval is useful to all interested stakeholders, it cannot mask the current regulatory system's inability to ensure human and environmental safety from pharma crops. The current regulatory system, as set forth in the Draft Guidance, does not ensure thorough environmental assessments before the planting of pharma crops nor does it adequately prevent those crops from contaminating the food supply. It also does not adequately ensure that no human will be exposed to harmful pharmaceutical substances in food. FDA and USDA should

[1] CSPI is a nonprofit education and advocacy organization that focuses on improving the safety and nutritional quality of our food supply and on reducing the damage caused by alcoholic beverages. CSPI seeks to promote health through educating the public about nutrition and alcohol; it represents citizens' interests before legislative, regulatory, and judicial bodies; and it works to ensure advances in science are used for the public good. CSPI is supported by the 800,000 member-subscribers to its Nutrition Action Healthletter and by foundation grants. CSPI receives no funding from industry or the federal government.

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revise the Draft Guidance to set forth a rigorous and robust regulatory system that ensures both human and environmental safety from this technology. Until such a system is put in place, no pharma crops should be grown out in the open.

The remainder of this comment letter sets forth the essential elements of a strong regulatory system for pharma crops as well as some specific comments on the Draft Guidance.[2]

I. The Key Components of a Rigorous and Robust System for Regulating the Human Health and Environmental Risks of Pharma Crops.

The recent incidents in Nebraska and Iowa involving pharma crops grown by Prodigene provide ample evidence of the need for USDA and FDA to use all their statutory authorities to regulate pharma crops. In particular, the regulatory system should do the following:

1. **Only allow the planting of pharma crops if the government issues a permit**. The regulatory system must put in place mandatory permitting requirements that must be complied with before the growing of any pharma crop. The permitting process should be transparent and allow for public participation before the issuance of the permit.

2. **Only issue a permit after a thorough environmental assessment of the potential risks from growing the pharma crop**. Before a permit is issued, the government should conduct a thorough environmental assessment of the potential effects of growing the pharma crop, including the effects from gene flow of the introduced gene and the effects of the transgenic protein on living species other than humans. The environmental assessment should comply with the National Environmental Policy Act, although for each individual permit, there may or may not be the need for an Environmental Impact Statement or an Environmental Assessment.

3. **The permits issued should require strict biological and physical confinement measures**. All permits should contain enforceable conditions requiring state-of-the-art confinement procedures. Those mandatory permit conditions should include isolation distances, geographic restrictions (such as not growing GE corn in parts of the country where commodity corn is grown), physical barriers (such as fences or greenhouses), the use of distinguishable varieties of the crop, biological confinement (such as male sterility) and so forth. The permit should also require extensive segregation procedures that ensure that none of the harvested materials can co-mingle with crops destined for human or animal consumption. When

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[2] This letter focuses on the human and environmental safety of the pharma crops and any unintended exposure to the pharmaceutical product. It does not address the regulatory oversight system for ensuring the safety of the drug product produced by the plant for its intended user.

using a food crop, the permit should have several redundant levels of confinement, even at the field trial level.

4. **The permits issued should require documentation of compliance with permit conditions**. All permits should contain education, certification, and documentation requirements. All persons working with pharma crops should be required to attend mandatory education seminars on the proper procedures to handle those crops and then obtain independent certification that they are qualified to participate in the handling of those crops. In addition, all permits should require the maintenance and then submittal to USDA of documentation verifying the compliance with permit obligations.

5. **The permits issued should require independent auditing of compliance with permit obligations**. As a condition of a permit, the developer should be required to hire a third-party independent auditor to oversee and assess compliance with permit obligations. That auditor should review documentation on compliance, regularly inspect the growing of the crop, and interview employees and contractors working with the crop. They should provide regular reports to FDA and USDA identifying all compliance issues.

6. **USDA and FDA should regularly inspect the production of the pharmaceutical in the plant**. As part of its regulation of pharma crops, both USDA and FDA should conduct regular, unannounced inspections of all facilities involved in the production of the pharmaceutical, from the laboratory to the farm to the manufacturing plants. Those inspections should occur after the crops have been harvested to prevent volunteer plants in future seasons. In addition, USDA and FDA should also inspect neighboring fields and crops to confirm that containment has been achieved.

7. **For pharma crops grown in food crops, there should be a mandatory pre-market food-safety approval process by FDA's Center for Food Safety and Applied Nutrition**. Although confinement measures need to strictly adhered to, they will never result in 100% containment over the long term. Thus, before any pharmaceutical is grown commercially in a food crop, FDA should conduct a thorough food-safety analysis to ensure that human exposure to the transgenic crop in the food supply will not result in any health risks. If additional legal authority is needed to implement this requirement, FDA and USDA should ask Congress to provide such authority.

II. Specific Comments to Draft Guidance

A. Relying on APHIS/BRS to conduct reviews of the environmental effects of growing pharma crops is inadequate.

On page 3, lines 203-213, the Draft Guidance states that APHIS/BRS will be responsible for identifying and evaluating any potential environmental effects of pharma crops. To date, there have been several hundred pharma crop plantings throughout the United States but APHIS/BRS has conducted detailed, individual environmental review for few, if any, of those plantings. For pharma crops, APHIS/BRS has not historically analyzed the non-target effects of growing pharma crops, or what effect pollen drift might have on similar crops or wild relatives. Thus, to rely on APHIS/BRS to conduct environmental assessments is to state that environmental safety issues will not be adequately analyzed before the planting of pharma crops.

B. Test methods for determining the presence of a bioengineered pharmaceutical in a plant should be required as part of the approval process.

Page 4, lines 272-274 of the Draft Guidance state that FDA/USDA "strongly recommend that you have tests available that can detect the presence of the target gene and the protein product in the raw agricultural commodity." This should not be a recommendation, but a requirement before a pharma crop is approved for commercial planting. In addition, the developer should be required to provide test methods for determining the presence of the gene or the protein product in finished food products.

C. A permit from APHIS/BRS should be required for all pharma crops.

Page 7, lines 423-426 state that "For **most** initial experiments and commercial uses of these plants, a USDA/AHPIS/BRS permit is needed." (emphasis added) Although that may be the government's current position, it should be revised to **require** a permit for **every** pharma crop planting. CSPI can think of no instance where it would be safe to plant a pharma crop in the open without the issuance of a permit and appropriate oversight by APHIS/BRS.

D. Physical confinement strategies should be required.

Page 9, lines 478-503 discuss the issue of physical confinement of the pharma crop while grown in the open. The Draft Guidance states that you "should consider" using readily distinguishable plant lines, restricting the expression of the product to a few specific tissues, or growing it in regions of the country where little or none of its food/feed counterpart is grown. For each of those physical confinement measures, UDSA/FDA should require those physical confinement measures as a condition of growing the crop, instead of leaving the decision of whether to implement up to the discretion of the developer. Pharma crops should not be grown near their food/feed counterparts and, where practicable, they should be grown only in plant lines that are physically distinguishable from their food/feed counterparts.

E. Personnel training and documentation should be required.

Page 10, lines 525-532 state that personnel "should" be trained before handling pharma crops and documentation "should" be maintained about field location and confinement measures

taken. Those actions should be mandated in permits issued by USDA or other documents from FDA authorizing the planting of pharma crops. Decisions about training and documentation should not be left up to the company developing the pharma crop.

F. Permits should mandate physical confinement, especially for food crops.

Page 10, lines 533-537 state that the developer consider "perimeter fencing to help exclude wildlife and escaped livestock." Where there is any chance of wildlife and livestock might come in contact with a pharma crop, perimeter fencing or other physical confinement should be mandated. In addition, perimeter fencing is not sufficient to prevent contact with some wildlife, such as birds and insects. When a pharma crop might be consumed by those species and have a detrimental effect, those crops should only be grown in greenhouses or with other confinement measures that eliminate any harmful non-target effects. Similarly, USDA and FDA should consider mandating that food crops containing a pharmaceutical only be grown under the strict physical containment of a greenhouse.

G. Only dedicated facilities should be used to process pharma crops.

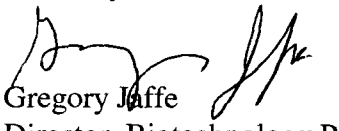
Page 10, lines 559-561 suggest that pharma crops can be processed in facilities used to process food or feed if there is prior consultation with USDA or FDA. Due to the fact that is impossible to completely clean equipment and prevent cross-contamination, those actions should not be allowed. Pharma crops should only be processed at facilities dedicated to those crops.

H. Only dedicated equipment should be used to handle pharma crops.

Page 14, line 732 states that the Draft Guidance recommends "the use of dedicated equipment" for harvesting pharma crops. This requirement should be mandatory to prevent any contamination of non-pharma varieties of the crop.

CSPI appreciates this opportunity to submit comments on FDA's Draft Guidance. If FDA would like additional information from CSPI about these comments, we would be happy to meet with you at your convenience.

Sincerely,



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