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January 6, 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 Monsanto Protein Technologies (MPT), a unit of Monsanto Company, 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Industry: Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals," (the Draft Guidance), the availability of which was announced in the September 12, 2002 edition of the Federal Register 67 Fed. Reg. 57828. Monsanto is involved in the development and commercialization of biotechnology-derived plants and plant products. MPT specifically is involved in the research and development of plant-made pharmaceutical (PMP) products in biotechnology-derived crops that are intended not to be in food or feed. We are committed to ensuring the safety of these products at all stages of development and production.

Coordinated Framework

Monsanto 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the efforts of the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA) to develop the Draft Guidance.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 necessary) 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 highest standards of health and environmental safety. Maintaining this approach will allow the benefits of plant-made pharmaceutical products to be made available to those in need, while facilitating the free flow of U.S. agricultural products in international trade.

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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 field tests of biotechnology-derived crops, including PMPs, suggests that this is an appropriate time to enhance existing guidance standards and procedures for the production of these products.

While the production of pharmaceuticals in biotechnology-derived crops is expected to increase availability of medicines and benefit patients, the federal government must maintain appropriate regulatory oversight, adjusting its requirements based on scientific developments and industry trends. In this context, we fully support FDA's proposed mandatory Premarket Biotechnology Notification (PBN) process[1] and we urge FDA's adoption of that regulation as soon as possible. The proposals set forth in the draft Guidance for Industry are a logical extension of the PBN proposal, and can be made mandatory based on that framework. These processes would increase public understanding and enhance consumer confidence in the existing safety precautions being taken by the agencies and the regulated community. We also believe that these measures will have a beneficial effect on international trade of U.S. agricultural products around the world.

Draft Guidance

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." Monsanto believes that the voluntary nature offered by the guidance document structure is customary and well understood in the pharmaceutical community, and is an appropriate means of outlining important scientific questions and information that should be addressed during the investigation and application process for drug and biologics subject to FDA and USDA's respective drug and biologic 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 establish these criteria in their 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 manufacturers of regulated products consider these issues, Monsanto believes that these environmental and confinement measures should also be addressed in a separate regulatory forum. A separate regulatory statement would provide clarity not only for the production of these regulated products, but also for other biotechnology crops that are intended not to be used for food or feed, such as plant-made industrial products (PMIPs).

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[1] "Premarket Notice Concerning Bioengineered Foods," 66 Fed. Reg. 4706, 4709 (Jan. 18, 2001).

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 APHIS'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.

Accordingly, Monsanto's comments on the Draft Guidance fall into two general categories. First, we provide broader suggestions for future regulation of these and similar crops by USDA under the PPA, building on the recommendations contained in the Draft Guidance. Second, we raise specific questions, comments and requests for clarification raised by the Draft Guidance (see Attachment 1). These will relate primarily to issues relating to the safety, purity and efficacy of the biological products being produced by PMP crops and regulated by FDA.

Recommendations for USDA Oversight Under the Plant Protection Act

Regulation of Industrial Crops

Crops that are developed through biotechnology for industrial use, and not intended for food or feed use (plant-made industrial plants, or PMIPs), present many of the same environmental and food safety issues as those developed through this technology to produce the regulated products discussed in the Draft Guidance. 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. These products should not be deregulated.

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, Monsanto believes that many of these

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[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.*

recommendations should also be addressed separately by APHIS, and be applied to both PMPs and PMIPs.

Detailed scientific and regulatory analyses confirm 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. Notwithstanding these facts, 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 out-crossing 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.) MPT decided in 1999 to grow its PMP crops that are intended not to be in food or feed only in areas of the country that are not centers of that crop's production (e.g. no corn-derived regulated articles in the mid-west corn belt).

Validated Testing Procedures

Monsanto supports action by USDA to require applicants for PMP and PMIP permits to make available testing methodologies to detect both the presence of the target gene and the protein product in the raw agricultural commodity. However, the detection of DNA in food or feed should be specified as obligating analysis for the protein product but should not constitute product adulteration under the FD&C Act.[6] Monsanto strongly supports the position repeatedly cited by FDA regarding the ubiquitous nature and safety of DNA.[7] Thus, detection of the protein product in food or feed should constitute product adulteration under the FD&C Act. Participation in a testing program should be a requirement for commercial approval. The testing program should include development of a validated assay and standards and a designated third party (such as the USDA) to act as a depository for validated assays and standards. (*See* Draft Guidance, ll. 268-274).

National Environmental Policy Act

Monsanto supports 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 Protection Act (NEPA) assessment. However, following well-established NEPA criteria, an environmental assessment (EA) would likely be appropriate, at a minimum, prior to the initial permitting of production at commercial scale of any PMP or PMIP.

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[6] 21 U.S.C. § 342

[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.").

Standard Operating Procedures

Monsanto supports PMP and PMIP permit conditions that require implementation of strict 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. MPT has previously and continues to submit detailed confinement plans and standard operating procedures with their permit applications. We strongly encourage the agency to treat these plans and procedures as permit conditions, subject to audit and inspection.

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). In our experience 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.

Dedicated Equipment

Monsanto agrees that dedicated equipment is necessary for planting and harvesting to help ensure that transgenic protein from PMPs and PMIPs do not enter the food/feed supply. Documentation of the use of dedicated equipment for these purposes should be a condition for obtaining an APHIS permit. 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 does not require "individually dedicated" equipment. Similarly, while the immediate transportation containers should be dedicated and contained, the larger transportation equipment need not be dedicated.

Dedicated Land

Monsanto supports the use of dedicated land in the field-testing and production of PMPs and PMIPs to help ensure that transgenic protein from these crops does 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 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 the land is to be used in the following growing season for the testing or production of PMPs or PMIPs, there may be no plant-back restrictions. If different PMPs or PMIPs are to be grown on the same land in subsequent years, appropriate quality assurance measures should be taken to ensure the safety, purity and efficacy of the end products.

Contract Growers

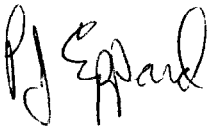
Monsanto supports permit conditions requiring PMPs and PMIPs to be grown exclusively under contract. In our experience a written contract provides added assurance that permit conditions and SOPs will be followed, appropriate training is in place and also facilitates USDA oversight.

Conclusions

Adequate agency resources that are sufficient to develop, administer and enforce them must support the proposed mandates for each agency. We urge each of the agencies to devote the funds and personnel necessary to appropriately support these initiatives. We also recognize that the work of the U.S. government should include dialogue and cooperation with governments around the world to assure consistent science-based regulations, including regulatory processes to establish the safety of biotechnology products.

Monsanto believes that a mandatory, science-based, coordinated approach should be used to regulate plant-made pharmaceutical and industrial products from crops intended not to be used in food or feed. A mandatory approach is consistent with existing USDA and FDA policy, as well as FDA's proposed PBN rule. We 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,



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