

Attachment 1

Docket No. 02D-0324

**Specific comments submitted by Monsanto Protein Technologies 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Bioengineered Plants for Use in Humans and Animals,” (the Draft Guidance)**

Section and line number citations refer to the Draft Guidance document, e.g., **IIC1** refers to Section **IIC1**.

IA. The scope of the document should be clarified to stipulate that the guidance also applies to university, private and government activities in this area, as well.

IB. Plant residue waste material issues should be specifically addressed in this section with continued management by APHIS.

IB. The Draft Guidance does not address non-field grown plants (greenhouse produced) and the general categorical exclusion for APHIS permitting for greenhouse planting. Monsanto recommends a continuation of the current policy for contained environment propagation and permitting for interstate movement.

IIC1. Monsanto recommends that there be expanded emphasis on analytical assays and testing programs for both DNA and protein produced in the raw agricultural commodity. A testing program should include a designated third party (such as the USDA) to act as a depository for validated assays and standards.

IIC1. We recommend that line 272, “..strongly recommends..” be changed to “The availability of tests to detect the presence of the target gene and the protein product in the raw agricultural commodity will be a requirement for obtaining a field release permit from APHIS (7 CFR 340)”, and that both DNA and protein identity tests are emphasized.

IIC2. Monsanto recommends specific references should be included for characterization of DNA such as International Conference on Harmonization (ICH), FDA guidance and points-to-consider, and comments regarding harmonization with EU guidance documents.

IIC3. We recommend changing “recommend” to “require” in line 306.

IIC4. We recommend that stability in transient systems, a sampling system to detect genetic drift after transfection, and a requirement to establish limits of genetic drift should be addressed.

IIC5. Monsanto recommends that an expanded definition be included in the Guidance of what constitutes a Master Seed Bank (MSB) and Working Seed Bank (WSB) relative to standard agronomic practices. Validation of a MSB and WSB plant host should be described or applicable existing Guidance documents referenced.

IIC5. Lines 373 – 375 should be changed to “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.”

IIC6. Monsanto requests further clarification regarding tissue distribution and the intent of this proposal. If this information is requested for issues of food safety, it may be better addressed under USDA Plant Protection Act oversight.

IIIB. In addition to the comments set forth on NEPA matters in the body of this letter, Monsanto suggests that this section contain general language describing those activities that would trigger the requirement of an EA, e.g., from FDA CBER Guidance for Industry, Environmental Assessment of Human and Biologics Applications, CMC 6.

IIIC1. There is a potential conflict between providing security of a field and the recommendation for some type of phenotypic characteristic to distinguish between transgenic and non-transgenic plants. We recommend that field site security take priority over phenotypic differentiation.

IIIC1. In line 487-488 the sentence should be modified to read “..or by use of genetic controls that restrict the conditions under which..”

IIIC1. We recommend that the language “... strongly recommend that you have tests available...” in line 497-498 should be changed to “The availability of tests to detect the presence of the target gene and the protein product in the raw agricultural commodity will be a requirement for obtaining a field release permit from APHIS under the PPA”.

IIIC1. In line 492-503 we recommend that a statement be included to a test certification and standardization program that resides within the USDA.

IIIC1. In line 492-503 we recommend inserting language specifically noting the use of SOP’s, batch records, and good agricultural practices as control measures to restrict unintended exposure of a regulated product.

IIIC1. In line 492-503 we recommend inserting a sentence: “The use of dedicated seed and plant handling facilities which are external to commodity grain channels will be a requirement for obtaining a field release permit from APHIS under the PPA”.

IIIC1. In line 492-503 Monsanto recommends inserting language specifically emphasizing that these processes are subject to APHIS inspection, especially during critical agronomic phases.

IIIC1. Contingency Plans for the Confinement Measures should be made a requirement for obtaining a field release permit from APHIS under the PPA. Those Plans should address response and mitigation procedures, and a sentinel testing process to confirm the effectiveness of field confinement procedures.

IIIC3. In line 533-534 we recommend clarification of the statement regarding the use of perimeter fencing. The use of fencing may be in conflict with security measures based on concealment. In our experience fencing is 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 fencing (containment).

IIIC6. Line 565-568 should be clarified to state that “regulated product” refers to non-viable plant material. 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.

IVB. Monsanto recommends that this section should include reference to a validated testing system that addresses consistent levels of target product in the plant host.

IVD3. In line 732 the sentence recommending to the use of dedicated equipment should be changed to “The use of dedicated equipment will be a requirement for obtaining a field release permit from APHIS 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.

IVD3. “Dedicated equipment” be defined as equipment used only in the production of plants used for producing transgenic proteins. Equipment can be used for different PMP or PMIP protein entities if there is a validated cleaning protocol and changeover protocol utilized prior to use. Equipment utilized for the production of PMP or PMIP proteins should never be used concurrently in a general food/feed agricultural environment.

IVD4. In line 751-759 we recommend that a statement such as: “dedicated equipment should be used for the transport and storage of food/feed related source material” be added to this section, and that a definition for dedicated equipment as in the previous section be used.

IVD4. In line 757-759 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 APHIS under the PPA.

IVD5. This section should be expanded to address container requirements for handling and processing PMP or PMIP plants to ensure that dedicated containers are utilized and not used interchangeably with standard food/feed operations.

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 host plant proteins and host plant DNA, as well as pesticides, herbicide, fungicide and fertilizer residues.

VB1. We recommend that line 940, “may be appropriate”, be changed to “shall be performed.”