January 9, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket No. 02D-0324

To whom it may concern:

The following comments are submitted by MERISTEM Therapeutics, a European biotechnology company member of the Biotechnology Industry organization (BIO) and member of the Plant-Made Pharmaceuticals (PMP) group, in response to the draft "Guidance for Industry: Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals."

As pioneer in Europe for the development of recombinant proteins produced in plants intended for therapeutic applications, MERISTEM Therapeutics feels that the guidelines which are currently implemented in European and US by the regulatory agencies are of strong concern. We have already carried out clinical trials in Europe with two recombinant proteins produced in bioengineered corn. This corn has been grown in Europe, Chile and United-States.

MERISTEM Therapeutics fully supports the efforts of the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA) to develop the Guidance for Industry related to Plant-Made Pharmaceuticals.

We consider that this guidance globally offers clear and pertinent recommendations and covers all the main aspects of the production of therapeutic recombinant proteins in plants.

Nevertheless, we would like to formulate some suggestions in order to facilitate the development of PMP, while guaranteeing the absence of risk for the food and feed industry.

MERISTEM Therapeutics supports the development of specific permit conditions for the release and importation of bioengineered plants intended for pharmaceutical products in order to offer stringent procedures during all stages of development and commercialization. As noticed in the Federal Actions document, USDA proposes, under its biotechnology regulations in 7 CFR part 340, to amend its regulations to provide criteria under which regulated articles intended for commodity uses may be allowable in

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commercial seed and commodities, if they pose no unacceptable risk to the environment or public health. MERISTEM Therapeutics considers that such regulations should be also applied to PMPs which cannot be considered hazardous by its sole final destination.

Such a permit should be given by the appropriate authorities based on the following criteria:

- Toxicological data on the transformed plant, the target protein and the genetic marker,
- Environmental data examining the potential risk created by the new plant,
- Existing analytical methods to detect of the regulated product,
- The plant species,
- The acreage of cultivation.

This evaluation should allow authorities to class PMPs into two confinement classes according to their potential risk for the environment and public health:

- Confinement Level 1: for plants obtaining a permit for growth in a controlled open environment, for which a low threshold of regulated product is admitted in seeds and commodities provided that data show no toxicological risk for human and animals nor environmental risk.
- Confinement Level 2: for plants that are required to be grown in a strictly controlled environment, in case of lack of data regarding the toxicological and environmental risks.

This proposal is inspired from the classification used for micro-organisms and in particular genetically transformed micro-organisms. We suggest adding a "Level 0" which would cover all safe plants which can be grown in a non controlled environment. Non regulated and deregulated plants (which have successfully performed all requirements) would of course be in this class. In our opinion, "Level 3" (higher risk than Level 2) should not be authorized for release in the environment.

To help understand this position, some examples of possible confinement requirements for levels 1 and 2 are given in table 1 below:

Requirements	Level 0	Level 1	Level 2
Permit	No	Yes	Yes
Good Agronomic Practices	Recommended	Yes	Yes
Confinement	No requirement	At least a two-layered barrier [1]	At least a three-layered barrier [1]
Fence	No	No	Recommended
Use of specific SOP's	No requirement	Yes	Yes
Use of trained operators	No requirement	Yes	Yes
Control of seed stock	Recommended	Yes	Yes
Control of pollen spread	No requirement	No requirement	Yes (sentinel plots) if crops of the same species are located below a minimal distance [2]

Table 1: example of possible requirements for levels 0, 1 and 2.

Requirements	Level 0	Level 1	Level 2
Validated methods to detect the target/marker gene and the target/marker protein	No requirement	Yes	Yes
Tolerance in food/feed crops of the regulated product	No requirement	Low threshold of tolerance admitted	< quantification level in 1 kg food crop
Use of dedicated equipment for culture and harvest	No requirement	Temporary dedicated. Possibility to change the use after applying a cleaning procedure and a visual checking	Strictly dedicated. Possibility to change the use after applying a cleaning procedure and after a documented control
Control of harvested material	Recommended	Specific labels on containers indicating that the material is not for food/feed purpose. Seals on containers. Reconciliation of the number of containers	Specific labels on containers indicating that the use is forbidden for food/feed purpose. Seals on containers applied on site (field). Reconciliation of the number of containers.
Post harvest control	No requirement	Destruction of volunteer plants	Destruction of volunteer plants. Fallow land during an appropriate time for the considered plant
Additional control of waste material/local and state regulation	No requirement	Inactivation of the target protein/marker	Inactivation of the target protein/marker with a validated method
Transportation on long distance	No requirement	In sealed containers	In systems with a double protection (e.g. bags + closed sealed container
Control at processing facilities	No requirement	No processing in facilities used for the production of food/feed without prior consultation with USDA-APHIS/BRS and FDA	No processing in facilities used for the production of food/feed

Table 1 (continuation): example of possible requirements for levels 0, 1 and 2.

Note 1: Example of multi-layered barriers to prevent inadvertent contamination of the food supply
Combination of two or three containment options, such as:

- Isolation distance,
- Culture in remote areas from crops of the same species
- Temporal isolation,
- Detasseling, castration of flowers
- Biological confinement: terminator technology
- Biological confinement: male sterile plant,
- Biological confinement: out-crossing plant
- Biological confinement: phenotypic maker
- Use of non food/feed plant.

Note 2: Minimal distance
This distance should be species dependant.

Such a classification could also be used for other genetically modified plants in development or commercial phase, such as:

- PMIP : Plant-made industrial products,
- PMN: Plant-made nutraceuticals.

We have also some minor suggestions which are summarized hereafter:

Page 4 Line 253

It would be valuable to explain why it is pertinent to state if the plant is of a species used for food or feed in a raw or processed form. We suggest the following modification:

> "Please state if the plant is of a species used for food or feed in a raw or processed form. **Plants used in a processed form will be preferable if the applicant can demonstrate that the target protein is degraded by the processing operation or becomes inactive.**"

Page 9 Lines 478-481

We think that strategies that allow the bioengineered pharmaceutical plant line to be readily distinguished from its food or feed counterpart should be considered as one of the multi-layered barriers to prevent inadvertent contamination of the food supply. It should not be mandatory and even necessary for PMP's which have proven a high level of safety (plants that could be classified in "Level 1" according to our classification).
The strategy of using genetic markers, though possible, is difficult to develop and needs a lot of time to be optimised. This strategy also needs to prove its safety towards the environment and public health. It can also modify the plant in a way that would not be appropriate for further processing and purification of the target protein, or can render the plant more sensitive to environmental conditions or pests for instance. Other techniques, such as the use of dyes during harvest may also be incompatible with the final use of the regulated product and will render more complex the purification process.

If we make a comparison with other pharmaceutical drugs, such strategies, that would allow to readily distinguish two different drugs in a multiproduct pharmaceutical facility, do not exist and are not required. The products are processed in segregated areas and with appropriate SOP's.

Therefore, we suggest some modifications in paragraph from line 478 to line 490:

> "When a plant species that is used for food or feed is bioengineered to produce a regulated product, **you should consider the use of multiple strategies that can help prevent inadvertent contamination of the food supply**. **Among these strategies, you may consider for instance**, the use of genetic markers that modify the physical appearance of the plant (e.g., a novel color or leaf pattern), or change the conditions under which a plant will grow (e.g., the use of an auxotrophic marker gene) in order to allow

the bioengineered pharmaceutical plant line to be readily distinguished from its food or feed counterpart. Such strategies might include the use. **You may also consider** strategies to reduce the likelihood of unintended exposure to a regulated product by restricting the expression of the bioengineered pharmaceutical product to a few specific plant tissues (e.g., the use of tissue specific promoters) or by restricting the conditions under which the product will be expressed (e.g., use of an inducible promoter). For such plants that outcross, you may want to consider growing them in regions of the country where little or none of its food/feed counterparts are grown."

Page 10 Line 543-547

We do not agree with your statement that ethanol production is incompatible with the use of residual materials from pharmaceutical plants. Ethanol results from three consecutive processes: pre-treatment of the plant at high temperature to liberate fermentable sugars and decrease the bioburden, fermentation and distillation. It is highly probable that the target protein will be degraded during these operations. And finally, it should also be eliminated by the distillation process, since high molecular weight molecules such as protein and peptides are not volatile.

Therefore we suggest that you remove "such as ethanol production" and replace "used for food or feed" by "found in food or feed" as written hereafter:

> "During transport, containers of harvested material should carry a label that clearly indicates that the material, including but not limited to seeds, leaves, roots, and stems, is not to be used for food or feed or for any purposes in which residual materials could be ***found in*** for food or feed, **unless you have specifically consulted with FDA for the use of this material in food or feed products**. ".

Page 10 Line 547-548

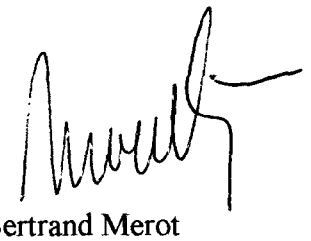
A precise reconciliation of the quantities leaving the fields (if expressed in kilograms or tons for instance) will be impossible for practical reasons and may lead to numerous discrepancies that will be difficult to investigate.
We suggest the following modification:

> "**Seals should be fixed on containers leaving the field and** a reconciliation of the **number of containers, or trucks, or tubs** leaving the fields and arriving at the process facility should be made."

We emphasize that any further oversight and regulation should be based on the best available 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.

We thank you for giving us this opportunity to comment.

Sincerely yours,



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