

Memorandum

Date February 5, 1992

Director, Center for Veterinary Medicine, HFV-1
Through: Director, Center for Food Safety and Applied Nutrition, HFF-1

Subject Regulation of Transgenic Plants - FDA Draft Federal Register Notice on Food Biotechnology

To Biotechnology Coordinator, HFF-300

Thank you for sending us the draft <u>Federal Register</u> Notice on Food Biotechnology (hereafter referred to as Notice), dated December 12, 1991. It is obvious that you have had a major task in synthesizing the scientific and regulatory issues.

In response to your question on how the agency should regulate genetically modified food plants, I and other scientists at CVM have concluded that there is ample scientific justification to support a pre-market review of these products. As you state in the Notice, the new methods of genetic modification permit the introduction of genes from a wider range of sources than possible by traditional breeding. The FDA will be confronted with new plant constituents that could be of a toxicological or environmental concern. The Notice further describes unintended or pleiotropic effects that pose unknown safety concerns. It has always been our position that the sponsor needs to generate the appropriate scientific information to demonstrate product safety to humans, animals and the environment.

A marked-up copy of the Notice with our comments will be provided to you directly by the Center's scientists. Generally, I would urge you to eliminate statements that suggest that the lack of information can be used as evidence for no regulatory concern. Examples of statements to this effect occur on p. 30 and p. 64 of the Notice. Furthermore, we believe that much of the detailed discussion on current scientific methods is not required in the Notice and, in fact, may be misleading. Sponsors may assume that if their transgenic product or methodology is not included in the Notice, that it is exempt from regulation. FDA regulatory policy must encompass both current and future techniques.

In addition to the human food safety and environmental concerns outlined in the appendices to the Notice, CVM believes that animal feeds derived from genetically modified plants present unique animal and food safety concerns. We list some of these concerns below:

 Unlike the human diet, a single plant product may constitute a significant portion of the animal diet. For instance, 50 - 75 percent of the diet of most domestic animals consists of field corn. Therefore, a change in nutrient or toxicant composition that is considered insignificant for human consumption may be a very significant change in the animal diet.

- 2) Animals consume plants, plant parts and plant byproducts that are not consumed by humans. For example, animals consume whole cottonseed and cottonseed meal, whereas humans consume only small amounts of cottonseed oil. Gossypol, a natural toxicant, is concentrated in the cotton seed meal during the production of cottonseed oil. Since plant byproducts represent an important feed source for animals, it is important to determine if significant concentrations of harmful plant constituents or toxicants are present in the transgenic plant byproducts.
- 3) The use of antibiotic-resistance genes as selectable markers in transgenic plants must be reviewed to determine the effect on animal therapeutics. For example, the enzyme product of the kan^r gene, aminoglycoside 3' phosphotransferase-II, inactivates the antibiotic, neomycin, which is used in feed and drinking water of animals..
- 4) Nutrient composition and availability of nutrients in feed are extremely important to the animal industry and animal health. Feed costs often represent 50 percent or more of the cost of producing animals. If a genetic modification made a higher percentage of a nutrient unavailable to the animal, it could have a major effect on animal health. For example, if an unintended effect of modification of soybeans was increased content of phytin, the amount of phosphorus available to the animal could be greatly reduced. Animal health problems could result unless the diet were supplemented with phosphorus.
- 5) Residues of plant constituents or toxicants in meat and milk products may pose human food safety problems. For example, increased levels of glucosinolates or erusic acid in rapeseed may produce a residue problem in edible products.

Because of the target animal, human food and environmental safety concerns delineated above and in the Notice, CVM proposes the acceptance of a modification of the primary regulatory scheme outlined in the Notice. The CVM proposed regulatory approach is as follows:

- 1) Firms expecting to market transgenic plants, for use in animal feed should contact Director, Division of Animal Feeds (DAF), HFV-220, Office of Surveillance and Compliance, Center for Veterinary Medicine, 7500 Standish Place, Rockville MD. 20855.
- 2) Firms requesting a decision on the status of their genetically modified plant should submit a data package under 21 CFR 570.30. DAF can make three determinations on a submission: a) the modified plant is not substantially different from traditional varieties, b) a Food Additive Petition (FAP) for the modified plant should be submitted under 21 CFR 571.1, or a GRAS Affirmation petition should be submitted under 21 CFR 570.35 or, c)

not enough information was submitted for a conclusion to be reached. For consultation and protocol reviews, firms should establish Investigational Applications under 21 CFR 570.17. DAF will apply the same review time frames as for an FAP.

- 3) For modified plants that CVM decides are not substantially different from traditional varieties, CVM will publish a notice of such finding in the Federal Register.
- 4) For transgenic plants that serve as food for both animals and humans, a decision must be made as to whether CFSAN or CVM will administer the document. The decision should be based on the primary use for the product. The administrator at the primary Center will have the responsibility of forwarding the submission to the secondary Center for a consulting review. Investigational animals to be used for human consumption would be authorized either under 21 CFR 170.17 or 21 CFR 570.17 by the respective Center.

If you have any questions, please contact Dr. Bill Price at (301) 295-8724.

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ATTACHMENT: REVISED FDA DRAFT FEDERAL REGISTER NOTICE ON FOOD BIOTECHNOLOGY

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4. Target animal safety feeding study.

Sponsors with products to be incorporated into animal feeds should conduct well controlled feeding studies in the target animal comparing the new plant variety to the conventional plant. study should be of sufficient size and duration to provide adequate statistical power to detect adverse effects should they occur. Only the highest normal feeding level of the feed product from the new plant variety would have to be tested. Common animal study parameters should be measured, including feed and water intake, weight gains, and blood clinical chemistry profiles. Gross pathology should be performed on preselected animals consuming the new plant variety and the conventional plant diets. Animals that die during the study should be necropsied to determine the cause of death. Additional testing may be necessary if it appears that residues from constituents of the new plant variety pose a risk to humans consuming animal products. Further guidance can be obtained from the Center for Veterinary medicine upon request.