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Draft Guidance for Industry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

by Friends of the Earth for Genetically Engineered Food Alert

Submitted to

Dockets Management Branch (HFA-305)
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Introduction

In July of 2002, Friends of the Earth (FoE) and Genetically Engineered Food Alert (GEFA) released the most comprehensive report to date on "biopharming" entitled ***Manufacturing Drugs and Chemicals in Crops: Biopharming Poses New Threats to Consumers, Farmers, Food Companies and the Environment***, a copy of which is appended as an integral part of this submission. Based on this report, we have concluded that the practice of engineering food crops to produce biopharmaceuticals and other compounds not meant for human food use poses too many risks – to human health, the environment and the economic interests of farmers and food companies – to be undertaken safely, whether outdoors or in "confined" systems. We believe that use of recombinant DNA technology for plant-based production of pharmaceuticals should only be pursued, if at all, in non-food crops or in plant cell cultures in strictly contained systems. Recombinant techniques, of course, have been widely used for 20 years to produce medically useful proteins in contained cell culture systems. These techniques can be used to produce most or all of the biopharmaceuticals envisioned for production in plants (though as detailed below, more careful testing is required even for these products). Alternative plant-production systems based on rhizosecretion (for example) can also be developed in strictly contained systems.

Adoption of our position by the FDA and USDA would make much of this proposed federal biopharm guidance document irrelevant. Thus, many of our comments seek to demonstrate the pressing need to prohibit biopharming as outlined above. Should the federal government continue to allow biopharmaceutical engineering to proceed, however ill-advised, the guidance document still has numerous recommendations that are inadequate or illogical in their construction. Our comments on these deficiencies should NOT be construed as an endorsement of biopharming contingent upon implementation of our recommendations.

Line number references (e.g. 479) refer to the guidance document. Relevant sections of FoE/GEFA's biopharm report, mentioned above, are cited as follows (e.g. FoE/GEFA 4.9.1).

Guidance not Adequate

A mere guidance document is not adequate to the task of regulating the practice of biopharming. As argued in a recent petition to the USDA, there is a pressing need for the USDA & FDA to implement state-of-the-art protective regulations and undertake a programmatic environmental impact statement with respect to genetically-engineered

pharmaceutical-producing plant varieties[1]. If done properly, we believe such an exercise would lead the government to adopt our position as outlined above. We also support the arguments presented in the cited petition for relaxing the USDA's overly restrictive protections for confidential business information (FoE/GEFA 6.3).

The guidance document has many weaknesses. There are far too many vague recommendations couched in language such as "you should consider the use of" (e.g. 479, 533-34), "you may want to consider" (e.g. 489), "we recommend that you" (e.g. 602), or at best "[w]e strongly recommend" (e.g. 497). The frequent suggestions that industry consult with the FDA or USDA on a case-by-case basis are likewise not reassuring (e.g. 501-03, 560-61, 569-71, 634-36, 941, 955-56, 974). In both cases – weak recommendations and recourse to *ad hoc* consultation & rulemaking – the FDA and USDA reveal their failure to adequately assess and formulate regulations for the pertinent issue. This approach allows applicant companies far too much leeway to concoct novel and untested schemes that may fall completely outside of measures considered or recommended in the guidance. In fact, the FDA and USDA explicitly welcome such schemes at the outset of the guidance document (116-17):

> *"An alternative approach may be used if such approach satisfies the requirements of applicable statutes and regulations."*

For example, if a company were to develop some "alternative approach" to permit it to make "dual-use" of a drug-plant hybrid for both drug production and food/feed use (FoE/GEFA 4.3), the FDA/USDA would presumably give it an *ad hoc* assessment, without public or external scientific review. Because "alternative approaches" are most likely new to the regulatory agencies and require case-by-case consideration, they cannot be given the measured and careful assessment entailed by a formal rule-making process; they evade both external scientific and public review as well.

Because of the many unique risks posed by biopharming, it is simply unacceptable to address them on such a casual, case-by-case basis, at the level of individual permit conditions, or through loose "guidance" recommendations. It will perhaps be argued that the broad variety of plant-made pharmaceuticals (PMPs) and situations in which they are grown make it impossible to establish standards that are both strict and general. Yet strict, mandatory standards can be developed that apply to particular crops, particular classes of PMPs, particular growing situations, etc. Failure to do so reveals the unwillingness of the government to anticipate and squarely confront challenging, problematic issues and design adequate regulations to deal with them – particularly cross-contamination of food crops.

[1] "Petition on Genetically Engineered Pharmaceutical-Producing Plant Varieties," submitted to the USDA by Center for Food Safety on behalf of Genetically Engineered Food Alert, December 16, 2002.

Excluded and Improperly Classified Compounds

The guidance apparently does not apply to transgenic plants engineered to produce research chemicals, industrial enzymes or other substances not intended for use as pharmaceuticals and/or not meant for human consumption (126-28). (If this interpretation is incorrect, the definition of "regulated product" should be modified to explicitly include such substances.) There are at least two obstacles here.

First, regulation of transgenic plants is improperly based on the "intended use" of the recombinant protein rather than its actual properties (FoE/GEFA 6.4.2). Thus, plants producing recombinant proteins intended for use as research chemicals can be grown outside of USDA's permit system and/or escape regulation by the FDA and/or EPA even if they possess pharmaceutical, insecticidal and/or known harmful properties (two examples are avidin and aprotinin, see FoE/GEFA, 4.5 and Appendices 2 & 3). "Regulated products" should be defined based on actual properties rather than intended uses.

The second obstacle is USDA's inconsistent, loosely applied classification system. Among the 300 some odd "phenotypes" used by USDA to classify recombinant, plant-produced proteins on its field trial website (www.nbiap.vt.edu/cfdocs/fieldtests1.cfm), one finds the catch-all category "novel protein," which provides no useful information about the nature of the protein[2]. In at least one case, the "novel protein" category is being applied to a substance (laccase, e.g. Permit 02-113-09n) that is explicitly intended for use as an "industrial enzyme" (see FoE/GEFA 4.10.2), another phenotype employed by USDA. In another case, it appears that a PMP now properly classified as "pharmaceutical" (aprotinin) was formerly listed as a novel protein (FoE/GEFA Appendix 3). A third example is the confusing use of the "antibody" phenotype, which USDA has made a category separate from, rather than a subset of, "pharmaceutical protein."

APHIS should precisely define, reformulate as necessary, and consistently apply the phenotypes such that they fully reflect the actual properties of the protein rather than merely its intended use. (This may mean applying several categories to a single recombinant compound.) The various phenotypes should be definitely assigned to either the notification or permit system. In addition, APHIS, the FDA and EPA should formulate clear and detailed procedures for the review appropriate to each phenotype, including which agencies take part in the review and the elements of that review. The

[2] Strictly speaking, ALL plant-produced recombinant proteins are novel, or should be considered so until full sequencing demonstrates otherwise.

review should take place before any field trial permit / notification is issued by APHIS. The information on phenotypes outlined above (assignment to notification or permit, elements of review required for each) should be made available on APHIS's website.

The novel protein category should be abolished because it provides no useful information and can be used to avoid specifying even the general nature of the protein (and APHIS / BRS provides the public with little enough information as it is). Antibodies should be made a subset of pharmaceutical proteins.

Recombinant plants that produce industrial enzymes and other substances not meant for human consumption that are nevertheless not covered under the current definition of "regulated product" should be: 1) Included in the scope of this guidance or subsequent regulations that supplant it; and 2) Subjected to USDA's permitting process rather than the weak notification system.

The Illusion of Zero Tolerance

Host plants (232-253)

If biopharming is to be permitted at all, APHIS / FDA should at the very least ban the use of food crops, which pose risks of contaminating the food supply through cross-pollination, volunteer growth the following season and other modes of seed dispersal. Corn and canola, in particular, should be banned, due to their high propensity for cross-pollination (FoE / GEFA 5.4).

Isolation of biopharm crops (489-90)

> *"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."*

While this measure would help reduce the risk of food / feed contamination via cross-pollination, it would do nothing to guard against the sort of volunteer contamination responsible for the ProdiGene episode in Nebraska, where biopharm corn volunteers contaminated soybeans grown on the same plot the following season. Other ways such contamination could occur are spillage of biopharm seed, biopharm seed carried to conventional fields in farm equipment, movement of biopharm seed by animals, and extreme weather events. The Royal Society of Canada notes that these many modes of

seed dispersal may well pose a greater risk of contamination than cross-pollination (FoE/GEFA 7.3.2)[3]. In addition, because the most popular biopharm plant, corn, is grown on 70-80 million acres across the country, it may be difficult to find sites which provide both adequate isolation from conventional corn and adequate growing conditions (soil quality, weather, adequate water, etc.). This problem will become more acute for biopharm/industrial crops growing high-demand compounds that necessitate substantial acreage in the thousands to hundreds of thousands of acres (FoE/GEFA 4.8, 4.10.2, 7.2.1)

[3] "Elements of Precaution: Recommendations for the Regulation of Food Biotechnology in Canada," An Expert Panel Report on the Future of Food Biotechnology, The Royal Society of Canada, p. 123. See http://www.rsc.ca/foodbiotechnology/indexEN.html.

Responsibility for confinement measures (456-63)

> "Regardless of whether the bioengineered pharmaceutical plants are grown and/or processed by you or on a contractual basis by other persons, manufacturing controls are your responsibility and should be documented clearly in standard operating procedures (SOPs), Outlines of Production, or other records, as appropriate…"

The food and grain supply have been contaminated several times now with recombinant proteins unapproved for human consumption. In at least two of those cases, breaks in the "chain of responsibility" for "manufacturing controls" was at fault. In the case of StarLink, the EPA delegated responsibility to Aventis, which in turn apparently relied on seed companies (chiefly Garst) to inform farmers of planting restrictions and the prohibition against food use. Many farmers never heard of these restrictions, or were given false information by Aventis and/or Garst (apparently to increase StarLink seed sales).[4] In the recent case of biopharm corn contamination of soybeans in Nebraska, on-the-ground responsibility for monitoring and preventing contamination was apparently divided amongst at least four players: USDA inspectors, ProdiGene, an agricultural consultant hired by ProdiGene to supervise the trial, and the farmer contracted by ProdiGene to actually grow the biopharm corn. A USDA inspector discovered volunteer growth, communicated this to ProdiGene, which in turn contacted the ag consultant, who didn't get the job done. A fifth player in this case was Nature. An unexpected hail storm reportedly opened up the soybean canopy, allowing light to reach the soil and trigger the sprouting of biopharm corn seeds left over from the previous year's harvest.[5]

Whoever is legally responsible, it is clear that in practical terms, responsibility for confinement measures is scattered among many players. This is a sure recipe for continued contamination episodes. It is difficult to envision a system, however, in which this chain of responsibility is tightened and shortened enough to do more than reduce somewhat the risk of contamination, especially with continued reliance on contract farmers.

Phenotypic markers (481-82)

[4] Ryberg, W. "Growers of biotech corn say they weren't warned: StarLink tags appear to indicate it's suitable for human food products," Des Moines Register, Oct. 25, 2000. See also: Freese, B. "The StarLink Affair," a report submitted to the EPA's Scientific Advisory Panel on behalf of Friends of the Earth, 2001, sections 10 & 11, Appendix VII. See www.foe.org/safefood/starlink.pdf

[5] Gillis, J. "Farmers Grow a Field of Dilemma: Drug-Making Crops' Potential Hindered by Fear of Tainted Food," The Washington Post, Dec. 23, 2002.

The guidance recommends that companies consider use of phenotypic markers (e.g. novel color or leaf pattern) when using food / feed crops to generate biopharmaceuticals in order to distinguish them from their conventional counterparts. It is true that an altered phenotype might help prevent those in the know from inadvertently mixing the biopharm crop in the food supply. If this phenotypic trait were reliably transferred and expressed in progeny in cases of cross-pollination, it might also help those in the know to single out biopharm volunteers resulting from inadvertent biopharm-conventional crop crosses. However, the utility of phenotypic markers would be limited to those aware of the connection between pharmaceutical and phenotype. Farmers, grain buyers, elevator operators, food processing workers, and others in the grain / food supply chain who are unaware of the connection would likely not be deterred from accidental misuse.

On the other hand, phenotypic markers greatly increase the risk of ***intentional*** misuse, because a malicious person who learns that a crop expressing a particular pharmaceutical substance has a particular phenotype could use this information to illegally harvest and then disseminate, cultivate or otherwise make illicit use of the crop. Despite the great emphasis on secrecy by government and industry with respect to all aspects of biopharming, it would be difficult to keep such knowledge of phenotypic markers secret (FoE / GEFA 7.4.3).

In short, phenotypic markers would *marginally* reduce the risk of inadvertent contamination, but greatly increase the chances of intentional misuse (especially given the industry's preferred practice of anonymously planting biopharm plots with no fences or other security measures).

Identification and security of biopharm plantings (532-34)

Identification of biopharm plots poses the same intractable dilemma as phenotypic markers. Identifying plots may reduce the risks of inadvertent misuse / contamination, and is of course also needed to alert neighboring farmers and the public to the risks of contamination, but it would increase the chances of intentional misuse. Enclosure of biopharm plots with high-security fences and the provision of alarms, floodlights, guards, etc. to prevent theft / illicit misuse would be extremely expensive, thus eroding the cost advantage that is the primary driving force behind biopharming. Such security measures would also be impractical for all but the tiniest plots. Compounds that only require small plantings to meet anticipated demand are likely to be biopharmaceuticals that are active at very low doses – that is, potent biopharmaceuticals (e.g. growth factors – see FoE / GEFA 4.9) – that definitely should not be grown out-of-doors at all due to potential health impacts on farmers from exposure during harvesting / processing and consumers from accidental contamination of food products. This is yet another reason

that biopharmaceuticals should only be produced in truly contained facilities, such as pharmaceutical plants.

Tests for biopharmaceutical gene and protein

(272-74; 497-501)

> *"We 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."*

A mere recommendation, however strong, is totally unacceptable here. In fact, in the interests of agency independence from the regulated company, the USDA or FDA should develop its own DNA primer sets and protein detection tests for each and every PMP before planting[6]. Failing this, the agencies should ***require*** that the company not only develop such tests, but turn them over to agency officials, who would then verify their accuracy and sensitivity and employ them for regular inspection rounds to test for possible contamination of any cross-compatible neighboring plants or weeds.

However, one must be realistic about the capability of protein tests. Expert advisors to the EPA who examined the StarLink issue in great depth decided that the ELISA assays used to measure Cry9C in processed foods were unreliable because food processing could denature or degrade it into a form not detectable by the assay.[7]. Likewise, it will probably be difficult or impossible to accurately measure biopharm proteins that slip into processed foods through contamination episodes. This would seem to make it impossible to set enforceable tolerances (FoE / GEFA 7.4.1).

Biopharm products containing viable seeds (649-50)

Due to high risks of uncontrolled propagation, the FDA should prohibit the commercialization and distribution of biopharm products containing viable seeds.

Dedicated versus dual-use equipment (732-34; 746-47)

The guidance merely recommends the use of dedicated equipment. Alternately, the applicant is encouraged to develop "equipment-cleaning procedures" and to document other uses of the equipment. Yet no equipment-cleaning procedure will be adequate to prevent carryover of biopharm seeds (e.g. corn) or completely eliminate engineered viral vectors (e.g. TMV). The editors of Nature Biotechnology ask the rhetorical question:

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[6] A similar recommendation was made in the aftermath of the StarLink debacle. See "Assessment of Additional Scientific Information Concerning StarLink Corn," FIFRA Scientific Advisory Panel, SAP Report No. 2002-09, p. 39. The FDA had ***not*** developed such tests for StarLink, was caught flat-footed by the StarLink contamination of the food supply, and had to call in Aventis CropScience to help it develop such tests.

[7] Ibid, pp. 12-14.

"Can we reasonably expect farmers to [clean] their agricultural equipment meticulously enough to remove all GM seed?"[8]

The answer, of course, is no – especially when plantings increase from a few acres to many thousands (FoE / GEFA 7.3.2). It should also be noted that the need for dedicated equipment, as well as other gene containment measures and expensive precision agriculture techniques, will price biopharming beyond the means of less wealthy, small and medium-sized farmers (FoE / GEFA 7.3.4).

Transfer and storage conditions (749 – 772)

The guidance requests only "confinement" of the harvested plant material during harvest, an implicit admission that complete "containment" is impossible.[9] The guidance also merely recommends that the biopharm plant material container be labeled. This should obviously be a requirement. There is no provision for dedicated silos or other storage containers, despite the obvious risk of food crop contamination with dual-use storage facilities. Dedicated storage facilities should be made a requirement.

Greenhouse growth (428-433)

The guidance exempts biopharm plants grown in "an enclosed building (e.g. greenhouse)" from an APHIS permit because they are generally considered to be "confined," yet at the same time admits that "control measures" must be in place "to eliminate the spread of pollen or seeds outside of the facility." It is entirely unclear how APHIS could ensure use of adequate "control measures" if such indoor trials do not require APHIS permits. Such indoor trials – especially if they make use of food crops – should require USDA permits and inspection visits.

Potential Health Impacts of Contamination Ignored

[8] "Going with the flow," editorial, Nature Biotechnology, Vol. 20, No. 6, June 2002.
[9] "Confinement" has come to replace the formerly-used "containment" in all aspects of GE crop regulation in order to reflect the fact that complete containment of gene flow is impossible.

Regulatory responsibility (177-213)

While contamination of food-grade crops with biopharmaceuticals is widely regarded as inevitable by leading experts (FoE / GEFA 4.7, 5.4, 6.3.3, 6.4.5), no one is taking responsibility for assessment of the potential human health impacts arising from such episodes. And it should not be presumed that any contamination that occurs would be intermittent or at low levels, the faulty assumption upon which the recent Office of Science and Technology Policy (OSTP) directive[10] is based. Both the risk of contamination and the extent of exposure increase greatly as plantings grow from field trials of a few acres to commercial plantings of many thousands. Clearly, the USDA has no competence or regulatory authority to undertake health assessments, despite the fact that it tried to do so once, tucked away in an environmental assessment of trichosanthin-producing tobacco (FoE / GEFA Appendix 4).

If open-air biopharming is not stopped (the best solution), the Food and Drug Administration must step up to the plate and conduct a thorough review of potential human health impacts before any more such plants are allowed to be planted. The review should cover at least two distinct areas: 1) Oral exposure (inadvertent ingestion by consumers); and 2) Inhalant / dermal exposure during growth, harvesting and processing (farmers, farm-workers, processing workers). A review of the available literature on the native form of the substance should be supplemented by thorough, independent studies on the potential health impacts of the plant-grown version (not a bacterial surrogate, which can be different, especially in terms of immunologic and allergenic properties). This review should be conducted before any planting is allowed.

Failing a complete ban on open-air biopharming, the USDA / FDA should prohibit cultivation of transgenic plants producing certain (classes of) substances for which appropriate data are not available or which are found to pose risks based on a thorough review. And it should be emphasized that the "early food safety assessment" procedures outlined in the OSTP directive (see footnote 10) must NOT be extended to field trials of biopharm plants[11], because they are not nearly comprehensive enough to detect potential allergenic or toxic effects of PMPs or food-grade crops contaminated by

[10] "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," Federal Register, Aug. 2, 2002. As presently written, the OSTP directive does not apply to biopharm plants, but we can expect some such scheme to be presented for PMPs, given the inevitability of contamination and the desire of the biotech & food industries to avoid the associated liability.

[11] The OSTP policy directs the USDA, FDA and EPA to establish voluntary procedures by which companies developing biotech plants can obtain a rubber-stamp approval (a.k.a. "early food safety assessment") alleging that novel biotech proteins in GE plants grown in field trials are safe. If implemented, this would permit contamination of food-grade crops with still largely untested GE field trial traits. While the OSTP policy does not apply to biopharm plants/PMPs, one can expect some such policy to be announced soon, given the impossibility of zero tolerance.

them. These superficial assessments are being promoted mainly as a means to absolve the biotech and food industries of liability for contamination episodes.

The government's performance thus far bodes ill for the future of biopharm regulation. Consider the following facts:

1) **Known health effects of current PMPs ignored:** At least three biopharm / industrial compounds grown for many years in biopharm corn are known to have deleterious effects on human health. Avidin is a corn-grown insecticidal protein that is known to cause Vitamin B deficiency upon ingestion (FoE / GEFA 4.5.1, Appendix 2). Aprotinin is a blood-clotting protein from a group of substances known to cause pancreatic disease in animals (and probably humans) upon ingestion (FoE / GEFA 4.5.2, Appendix 3). Trypsin is an inhalant allergen known to cause occupational asthma in workers exposed to it, and thus could pose a similar risk to farmers and farm-workers who harvest it (corn dust & pollen) (FoE / GEFA 4.10.1). The abortion-inducing protein trichosanthin was generated in tobacco by means of an engineered virus that can also infect tomatoes, peppers, potatoes and related food crops (FoE / GEFA Appendix 4). As far as we know, the FDA has failed to assess these or any other biopharm proteins for potential health impacts.

2) **No restrictions on host plants:** There have been no regulations to restrict the choice of host plants for biopharm production to non-food crops. In fact, USDA has permitted one of the worst crops in terms of contamination (promiscuous corn) to become by far the favorite crop choice for biopharmers (70% of biopharm field trials have made use of corn) (FoE / GEFA 5.4.1, 6.2).

3) **Deficient oversight:** The USDA does not conduct ANY inspection of 90% of field trial sites involving plants grown under its "notification" system, which includes plants engineered with industrial chemicals (personal communication, James White, USDA). The USDA allowed 500 bushels of biopharm corn-contaminated soybeans to get mixed with 1,000 times that amount of clean soy in an Aurora, Nebraska grain elevator, one step away from the food / feed chain, then had the brazenness to declare this a regulatory success.

Exposure to biopharm proteins through dual use (563-579)

While the guidance recommends "disposal [of biopharm plant material] in a manner to ensure that the material will not enter the human or animal food chain," – it then immediately creates a loophole – "unless you have specifically consulted with FDA for the use of this material in food or feed products." This loophole is the only reference in the entire guidance to an extremely troubling aspect of biopharming – dual use of biopharm crops for both drug and food / feed purposes (see also FoE / GEFA 4.3).

First of all, we should recognize that what is presented here as an exception to the general rule of disposal would likely become the norm for most biopharm and industrial crops, for several reasons:

1) **Dual-use – an offer too good to refuse:** Because dual-use would offer companies substantial benefits – both avoidance of disposal expenses and profit from sale of biopharm plant byproducts into the food / feed chain – in many cases they will aggressively lobby the FDA to approve dual-use under this loophole.

2) **Mountains of waste:** This is especially true for high-volume compounds requiring, say, thousands of acres to meet demand. For example, contraceptive corn would require tens of thousands of acres (FoE / GEFA 4.8), while laccase corn (according to ProdiGene's projections) could be planted on 200,000 to 2 million acres (4.10.2). To give an idea of the magnitude of the problem – and the cost savings / profit from dual-use versus disposal – consider that just 1,000 acres of corn yield over 8 million pounds of corn kernels alone, not counting other parts of the plant. And since the extracted biopharm protein will represent an insignificant proportion of the corn kernel, nearly 8 million pounds of kernel byproduct, some of it suspended in column wash solutions and such, would have to be "treated to inactivate the regulated product," and then disposed of. How much will this cost? On the other hand, how much profit could be made by diverting millions of pounds of byproducts into the food and feed chain?

3) **Approval of dual-use:** We will presumably be told that dual-use will never be permitted without studies to demonstrate complete extraction of the biopharmaceutical and / or no adverse effects on animal / human health from any biopharmaceutical residues that remain in byproducts. Yet this is mere speculation. The FDA says absolutely nothing about criteria to be met for dual use in the guidance, preferring to deal with this huge issue on its own undisclosed terms on an *ad hoc* basis. Even if a laboratory or pilot-scale processing study should demonstrate reasonably complete extraction, should consumers and farmers depend on biopharm processors to consistently remove such potentially dangerous residues from materials entering the food and / or feed supply? To take one scenario. Use of biopharm corn byproducts for ethanol production would also generate corn gluten, consisting mainly of corn proteins, which might then be sold into the feed and food chains. Any unextracted biopharm protein residue would be concentrated in gluten.

4) **Other biopharm plant material:** It is unclear whether or not the guidance even addresses the disposition of those parts of the biopharm plant that do not enter into the purification process.

*"In-process wastes (e.g. column wash solutions, diafiltration solutions, etc.), rejected in-process material, and **residual source plant material from the purification process** should be treated to inactivate the regulated product prior to disposal, as appropriate." (my emphasis)*

In this sentence, the phrase in boldface could be interpreted to apply only to those parts of the plant that are processed for extraction of the biopharmaceutical. In the case of corn, companies will normally process only kernels, not stalks, leaves, roots, etc. (If this interpretation is incorrect, the guidance should be amended to ***explicitly*** require harvest of, and inactivation of the regulated product in, ALL biopharm plant tissues.) If this interpretation is correct, the USDA / FDA need to address the troublesome issue of the biopharm protein present in millions of pounds of non-processed crop residues (see "'Tissue-specific' promoters" below, as well as FoE / GEFA 5.6.3). Will they be incinerated, composted? Will there by any provision for inactivation of the regulated product in such residues?

"Tissue-specific" promoters (485-87)

Use of so-called "tissue-specific" promoters is recommended to "reduce the likelihood of unintended exposure." More careful scientists employ the term "tissue-preferred" promoter in recognition of the fact that expression of the target protein is seldom or never limited to the target tissue; as even ProdiGene admits: "some expression may occur in other parts of the plant." There is also evidence that varying cellular and environmental conditions can reduce the tissue specificity of a tissue-preferred promoter (FoE / GEFA 5.6.3). USDA / FDA are encouraged to adopt the more accurate term "tissue-preferred promoter" in place of the misleading "tissue-specific promoter," and not to rely on this mechanism as a means of preventing unintended exposure.

Viral-vectored transfection systems (341-369)

Viral-vectored transfection systems should not be permitted at all for biopharmaceutical production in plants due to our vast ignorance of viruses in general, their easy mutability, and the potential for infecting a related food crop with the biopharm gene. This latter consideration applies particularly to the tobacco-tobacco mosaic virus (TMV) system most commonly used in biopharm experimentation, since TMV is known to infect solanaceous family relatives of tobacco such as tomatoes, peppers, eggplant and potatoes, as well as numerous weeds. (For a detailed assessment of a biopharm field trial involving TMV-vectored infection of tobacco with the toxic protein trichosanthin, see FoE / GEFA Appendix 4.)

At the very least: 1) No viral vectors for which the "gene(s) involved in vector transmission" (356) is / are unknown should be permitted; and 2) No viral vector which has not been tested thoroughly and found negative for potential "synergistic or transcapsidation interactions with other viruses" in laboratory situations should be permitted.

Potential Health Impacts on Farm & Processing Workers Ignored

The guidance has nothing to say about measures to protect farmers and farm-workers who will be exposed to biopharmaceutical proteins through inhalation of crop dust & pollen, skin contact and ingestion (FoE / GEFA 7.7). This is not surprising, since the USDA and FDA have apparently given no thought at all to farm & processing workers. Amazingly, the entire 240-page transcript of the two-day "Plant-Derived Biologics Meeting" in Ames, Iowa – the major meeting held in April of 2000 to gather information to help formulate this guidance document – contains only a single brief discussion of possible health risks to farmers. An FDA official asks an industry representative whether his company would inform a contract farmer of a [potentially dangerous] PMP he is growing, "or would that be a problem?" (see FoE / GEFA 7.7 for more on this). Here's the situation: Government regulator, charged with protecting public health, timidly asks the regulated company whether it will inform a farmer of a potentially dangerous product the company has put into his / her hands. Unfortunately, the timid attitude adopted by this FDA official (who is to be commended for at least raising the issue!) is surpassed by the guidance document, whose silence on farm and processing worker health speaks more loudly than any words about how little farmers' health means to government regulators, including those at the USDA whose job is supposedly to promote and protect their interests.

There is also no evidence to suggest that USDA or FDA has bothered to consult with farmers or representatives of genuine farmers' groups (as opposed to agribusiness lobbyists) about biopharming. There was not a single farmer's voice at the Ames meeting mentioned above.

In the interests of farm & processing worker health, companies should be required to:

1) Disclose the identity and any known harmful properties of the biopharmaceutical or industrial compound to farmers, farm-workers, processors, and others who will come into contact with it before any contracts are signed or exposure has occurred;

2) Provide all farm and processing workers with any necessary protective equipment, in line with government-approved standards, adequate to protect them from any adverse health impacts associated with the given compounds;

3) Contract independent and qualified health professionals to test all farm and processing workers who come into contact with the PMP for any adverse health impacts, including immunogenic or allergic reactions and toxic effects.

Such testing is necessary to protect front-line agricultural and processing workers, and it could have further benefits. Health impacts in these high-risk, high-exposure groups can signal potential risks to consumers. In fact, there is evidence that sensitization to an allergen via inhalation can predispose to later development of food allergies.[12] Such information could have proven valuable in the context of the StarLink corn debacle. Expert advisors to the EPA requested several times that seed company workers who grew and sold StarLink corn (from Garst Seed Company) be tested for allergies to Cry9C. Besides its obvious benefit to the workers, such testing would have helped the advisors determine whether Cry9C posed a threat to consumers. Neither Aventis nor the government saw fit to do this testing[13], and it is still uncertain whether Cry9C is a food allergen.

To take one contemporary example (FoE/GEFA 4.10.1). Trypsin (an industrial enzyme) was reportedly grown in hundreds of acres of corn in 2002, despite the fact that the conventional version is known to cause occupational asthma. The USDA and FDA, however, have refused to recognize the potential risks of trypsin exposure, refused to make an assessment of potential farm-worker health impacts. Apparently, the agencies prefer to let companies conduct uncontrolled experiments on their workers and contract farmers. Trypsin is just one of many industrial enzymes that may pose similar threats and which are anticipated to be grown on thousands to millions of acres (FoE/GEFA 4.8, 4.10.2, 7.2.1).

Economic Impacts of Biopharming on Farmers & Food Industry Ignored

[12] Bernstein et al (2002). "Clinical and laboratory investigation of allergy to genetically modified foods," Environmental Health Perspectives, ehponline.org, online December 19, 2002, pp. 28-35.
[13] Freese, B. "The StarLink Affair," op. cit., section 7.2 (see footnote 4)

No official venues for consideration of economic impacts

Unfortunately, there does not appear to be any official government venue for consideration of the economic impacts of biopharming – in particular, the economic consequences of inevitable contamination episodes – on American farmers. This is totally unacceptable. Instead, this vitally important issue is left to be thrashed out in the political arena, with financially-interested industry trade groups and woefully ill-informed politicians making decisions that could – and almost certainly will – have billion-dollar liability and export implications for American farmers and food companies. Likewise, there has been no official forum in which farmers – as opposed to agribusiness lobby groups – can bring their unique, on-the-ground perspectives to bear on the real risks of biopharm crops contaminating the food supply.

The USDA is urged to hold a high-level public forum on biopharming that addresses not only containment, consumer health & environmental issues, but also the question of the economic impacts of this enterprise on American agriculture, the food industry, and small/medium-size farmers. Such a forum should include not only scientists, health specialists, economists and agronomists, but also environmental/food safety advocates and, most importantly, farmers and representatives of agricultural organizations (such as American Corn Growers Association, National Farmers Union and National Family Farm Coalition) that actually represent small and medium-size farmers.

Survey attitudes of affected groups and conduct economic analysis of impacts of biopharming

> "…measures should be in place to ensure that there is no inadvertent mixing of the bioengineered plant material with plant material intended for food or feed use." (268-270)

This is one of many statements in the guidance upholding the illusion of zero tolerance. In fact, the only way to ensure the zero tolerance implied in this statement is to ban open-air biopharming, particularly in food crops. If USDA/FDA choose not to do this, the agencies should at the very least initiate an honest, wide-ranging public dialogue to ascertain the attitudes of the public, the farming community, the food industry, public interest groups, etc. towards the inevitable episodes of biopharmaceutical contamination of the food supply that will occur with continuation of current policies.

The agencies should also conduct extensive consultations with grain handlers and traders in relevant crops – both American and foreign (particularly those in important export markets) – to the same end. This information should be used to develop detailed estimates of food company liability, crop export losses, economic impacts on the farming community, government expenditures (= taxpayer subsidies) for needed interventions (e.g. the USDA's purchase of StarLink-contaminated seed stock cost taxpayers tens of millions of dollars), and other adverse effects of such contamination episodes, which estimates should be made public. Such analyses could employ data generated on the continuing StarLink contamination episodes as a reference. (FoE / GEFA 7.4 & 7.5).

Biopharming will inevitably harm American agriculture and public trust in the food supply, but without honest dialogue and modeling of this sort, the magnitude of such harm will undoubtedly be greater than it would otherwise be.

Control and liability issues (518-537)

(See also "Responsibility for Confinement Measures" above (456-63))

> "You must … have control over the growing process from planting through harvesting and over the disposition of remaining crops and / or crop residue and, if required, over the subsequent use of the field if for growth of food or feed or as a pasture during subsequent seasons."

The diffusion of on-the-ground responsibility for the growing process among many players (discussed under "Responsibility for Confinement Measures" above) creates numerous opportunities for communication breakdown, misunderstandings, and intentional misuse, any of which can easily result in contamination episodes. At present, most biopharm field trials are conducted by contract farmers with only occasional visits by company officials, and few if any inspection visits by government inspectors. This situation cannot by any stretch of the imagination be described as "control over the growing process" by the company. Once again, the USDA / FDA show no understanding of the real world of farming, human fallibility, conflicts of interest, weather, etc., preferring the legal fantasy of "control" to the facts on the ground, which completely belie the notion that biopharming is controllable.

Therefore, the phrase "have control over" should be replaced by "bear liability for," so that at the very least contract farmers will not be held liable for the inevitable contamination mishaps that will occur, no matter how careful the farmer's stewardship.

Biopharming Poses Novel Threats to Drug Safety

Use of pesticides, herbicides, fungicides & other agricultural chemicals (699-717; 943-956)

Biopharming introduces a truly novel threat to the world of pharmaceutical production: the potential for residues of toxic agricultural chemicals in the ***drug*** supply. Never before have pharmaceutical users been confronted with the prospect of eating, applying or injecting a drug laced with pesticides, herbicides or fungicides. What does the guidance have to say about this important subject?

Information requested by FDA:

1) What pesticides, etc. the company plans to use and any limits on such use
2) What pests are expected

Recommendations made by FDA:

3) Develop standard operating procedures for recording pesticide applications
4) Pest-control measures should be in accordance with good agricultural practices
5) Only EPA-approved pesticides, etc. should be used
6) Companies should establish tolerances (i.e. maximum allowable levels) for "any pesticide, herbicide, and/or fungicide residues anticipated to be present, justify the safety of those amounts ***under conditions of anticipated use of the pharmaceutical***, and demonstrate that the final product does not exceed those limits" (my emphasis)
7) Applicants should check with EPA "if you have questions regarding the use or safety of pesticides…" (FDA helpfully cites the EPA's Pesticide Product Information Service webpage)

This paltry guidance does almost nothing to proactively protect pharmaceutical users from toxic residues in drugs. To understand this, consider the following:

Greater incentives for toxic chemical use on biopharm crops

First of all, biopharm crops will be extremely valuable, in some cases worth several million dollars per acre to the biopharm company.[14] This value creates strong incentives for protecting the crop in the field and in storage from insect pests, mold

[14] It should be remembered that contract farmers will likely receive very little of this value. For instance, ProdiGene has offered contract farmers at most 40% above commodity prices (about $1/bushel) for biopharm corn, and will not even guarantee this tiny premium.

infestation, disease and competing weeds by whatever means possible. A contract farmer or biopharm company that relies on biopharming for a substantial part of his/her/its income will be especially anxious to ensure that the crop is not rendered unacceptable due to insect damage, contaminating mold or mold toxin, etc. Thus, all other things being equal, pesticides, herbicides and fungicides are more likely to be applied to biopharm crops than to lower-value food & feed crops (FoE/GEFA 4.2).

Diffusion of on-the-ground responsibility opens door to misuse

The diffusion of responsibility for biopharm crop production among company officials, contract farmers and agricultural consultants – and the dearth of government oversight – open up numerous opportunities for unprescribed use of these chemicals. If an unprescribed pesticide is applied, it may not be eliminated during extraction and purification.

Many ag chemicals implicated in cancer and/or hormonal disruption

Abundant research has shown that many registered pesticides are proven or suspected carcinogens; more recent studies have identified at least 56 pesticides as endocrine disrupters[15], which can have potent effects on brain & sexual development, the immune system, thyroid function, etc. at extremely low levels.

Injected drugs a particular concern

Pesticide residues are of particular concern for PMPs intended for injection. For one, pesticide residues injected into muscle tissue or infused directly into the blood stream are more likely to be active at far lower doses than if consumed or applied dermally, because they bypass the partial protection afforded by gastrointestinal tract or skin. In addition, there has likely been little research done on the effects of most pesticides upon injection or infusion, since exposure to agricultural chemicals in foods/crops is limited mainly to the oral (consumer) and dermal/inhalant (agricultural worker) routes.

Synergistic effects unstudied, ignored

Finally, pesticides residues might have synergistic effects with each other, or with the PMP.

Given these serious and in many cases ***novel*** risks, the guidance is ridiculously weak. Some questions that need to be answered:

1) Why does our Food and Drug Administration defer to the Environmental Protection Agency to provide applicants with information about the potential risks of toxic chemical residues contaminating ***drugs***, especially drugs meant for injection? Is the EPA qualified to give guidance on pesticide-laced biopharmaceuticals? (point 7 above)

[15] See www.ourstolenfuture.org/basics/chemlist.htm

2) Doesn't the FDA find ***any*** EPA-approved pesticides too risky for biopharmaceutical crop use, especially those with hormonal effects? (points 1 & 5) If so, why aren't they prohibited?

3) Of what relevance are "pest-control measures … in accordance with good agricultural practices for the growth of ***food*** crops…" to the issue of pesticides residues in ***drugs***, especially injected drugs? (point 4)

4) Since when has private industry been put in charge of establishing tolerances for pesticide residues? (Obviously, EPA-prescribed tolerances for pesticide residues on ***foods*** cannot be automatically adopted for residues in ***biologics***.) (point 6)

5) What studies will the FDA require from companies to "justify the safety of those amounts [tolerances] ***under conditions of anticipated use of the pharmaceutical***," especially when the intended route of administration is parenteral? Will human experiments be conducted to determine the "safe" levels of injected pesticides?

6) What sort of inspection/testing regime will FDA establish for pesticide residues in biologics? (points 3 & 6)

Once again, the FDA's guidance raises more questions than it answers. Instead of a careful and thorough assessment of the novel issue of pesticide residues in biologics, the agency apparently prefers to give industry free reign to do what it wants, delegate the most difficult questions to a sister agency (EPA) with no experience in the field of drugs, and to bungle along with it usual *ad hoc*, case-by-case assessments of industry-formulated schemes for both biopharm crop pesticide use and removal of pesticides from PMPs.

Characterization (785-808)

The applicant should be required to fully characterize the nucleotide and amino acid sequences of the biopharmaceutical gene and its protein product ***as introduced into the plant genome and expressed by the plant.*** These sequences should be compared to the native versions of the gene/protein (for plant-made "animal" or "human" biologics). Identification of the insertion site in the plant genome, and characterization of plant DNA near the insertion site, should also be required. Non-targeted profiling techniques to detect the levels of a wide range of plant constituents (preferably, all) should be undertaken as well, especially for edible biologics. This information could prove to be vital for understanding any adverse, unintended effects of the PMP (FoE/GEFA Appendix 1).

Considerations for testing (896-990)

The FDA should under no circumstances allow the use of surrogate versions of the bioengineered PMP generated in organisms such as bacteria for the purposes of animal testing or human (pre-)clinical trials, due to the potential for important differences (e.g. immunologic, allergenic) between surrogate and plant-produced proteins. (This is, unfortunately, standard procedure for testing of most recombinant, plant-produced proteins, such as the insecticidal toxins expressed by Bt crops.[16]) Likewise, the FDA should not rely on "the extent of [sic] structurally and pharmacologically comparable products for which there is clinical experience" in deciding on the extent of pre-clinical testing needed for the PMP, especially if the comparable products in question are extracted from their native [mammalian] host or generated in non-plant systems. On the contrary, due to the many unique aspects of plant expression systems (e.g. unique glycosylation and post-translational modifications) and the near total lack of control over "production conditions" (i.e. rainfall, heat, pest attack, mold infestation, etc., etc.), PMPs should be fully tested as novel drugs in every case, regardless of what "comparators" already exist. In fact, it would seem advisable to subject every batch of PMP derived from plants with different genetic backgrounds or from plants grown in differing environments (including extreme conditions) to a full and stringent set of tests to determine what changes occur in the PMP under varying conditions.

Immunogenicity and allergenicity (964-990)

A growing body of evidence demonstrates puzzling, unpredicted and in some cases dangerous immunogenic responses to biopharmaceuticals produced in engineered cell cultures. Such reactions may lessen or eliminate the drug's potency, induce allergic responses, or even cause auto-immune dysfunction in which the body's natural version of the drug is also inactivated.[17] Engineered drugs that have elicited immune reactions associated with reduced (or loss of) efficacy include the blood-clotting Factor VIII and the multiple sclerosis drug beta-interferon. Auto-immune dysfunction has also been observed. A version of a platelet-inducer known as megakaryocyte growth and development factor (MGDF) produced by Amgen was discontinued in clinical trials because some patients receiving the drug mounted an immune attack on both Amgen's MGDF and their own natural version of MGDF, resulting in bleeding. A similar phenomenon has been observed with several companies' engineered versions of erythropoietin, a top-selling biotech drug that stimulates red blood cell production

[16] Freese, B. (2001). "A Critique of the EPA's Decision to Re-Register Bt Crops and an Examination of the Potential Allergenicity of Bt Proteins," adapted from comments of Friends of the Earth to the EPA, Docket No. OOP-00678B, Dec. 9, 2002. See www.foe.org/safefood/comments.pdf.

[17] Pollack, A. "Rebellious bodies dim the glow of 'natural' biotech drugs," The New York Times, July 30, 2002.

(most cases involve Johnson & Johnson's Eprex).[18] This adverse effect was caught only after Eprex had been on the market for years.

These immune system responses have taken scientists and regulators alike by surprise. Dr. Burt Adelman, head of research & development at the biotech firm Biogen, found the immune reactions to MGDF "stunning."

> *"The conventional wisdom had been that this was a theoretical risk … nobody saw it coming. If you're in my business, it's really unnerving."*[19]

One problem is that even slight alterations in the processes used to make these drugs in tightly-controlled fermentation tanks can cause significant but difficult-to-detect differences in the final product. According to the FDA's Chris Joneckis, speaking at a May 2002 FDA workshop:

> *"Despite best efforts to detect product differences and predict the impact of manufacturing changes, these surprises do continue to occur."*[20]

The biggest surprise thus far has involved biotech's flagship product Eprex, which is used to stimulate production of red blood cells to treat anemia. Eprex has been implicated in up to 160 cases of red cell aplasia. The aplasia (virtual shutdown of red blood cell production) results from disablement of both Eprex and the body's natural version of the substance by the immune system. Despite four years of investigation, it is not known how Eprex induces red cell aplasia in these patients.

Like many biotech drugs, Eprex is generated in mammalian cell culture. Drugs generated in mammalian cells are generally expected to cause fewer such immunogenic reactions because of the similar way in which all mammalian (including human) cells process the proteins they produce. Plants process proteins differently than animals; for instance, they attach different sugar groups to the surface of proteins, which can make even a "human" PMP appear foreign to the immune system, increasing the risks of immunogenic and allergic reactions (FoE/GEFA 4.1).

Given the recent surprising incidence of immunogenic reactions to biotech pharmaceuticals, and the increased risks associated with PMPs, it is disappointing to see just four inadequate paragraphs devoted to allergenicity and immunogenicity in the guidance. The FDA should:

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[18] Tagliabue, J. "Mystery effect in biotech drug puts its maker on defensive, The New York Times, Oct. 2, 2002.
[19] As quoted in: Aoki, N. "Protein therapies spark scrutiny: researchers weigh potential risk of immune responses," The Boston Globe, Nov. 27, 2002.
[20] Transcript of "Comparability Studies for Human Plasma-Derived Therapeutics," FDA CBER workshop, May 30, 2002, p. 42.

1) Develop a robust model for testing PMPs for potential allergenicity and immunogenicity before any more field tests or clinical trials are allowed to proceed, taking special account of the factors that make plant expression systems more likely to generate problematic proteins;

2) Demand that ***all*** PMPs be tested for allergenicity and immunogenicity rather than let applicants "assess the need for allergenicity testing for each product…" Many products might never be tested for allergenicity under this guidance.

3) Require full characterization of all antigenic determinants, especially sequencing of N-glycans, rather than vaguely recommend an evaluation of "the final product for antigenic determinants…," which could be interpreted to mean that the applicant need only report on the presence of such determinants, not elucidate their structure. As adverse reactions to biotech proteins (including PMPs) accumulate, detailed structural data (e.g. precise sequence of glycosyl groups) might help in determining the causes.

4) Refer to established protocols for allergenicity testing of novel bioengineered proteins in developing such models for PMPs (in the case of oral biologics, the FAO-WHO 2001 protocol[21] could serve as a model). The FDA completely fails to discuss, mention or even cite any of these protocols, a puzzling omission given the agency's past involvement in promoting development of these testing schemes.

Allergy issues for biopharmaceuticals in whole fruit or vegetable products

(634-36)

The issue of native allergens in biopharm plants and plant products meant for oral use should not be dealt with ***exclusively*** on a case-by-case basis. This is because similar allergenic issues will arise for each crop, regardless of the biopharmaceutical it produces, and it should be possible to establish standardized procedures to ensure the most complete possible removal/inactivation of native allergens. Yet because different transformation events could give rise to unintended effects that in some cases may raise native allergen levels, the standard procedures may have to be amended on a case-by-case basis in light of detailed analyses of the biopharm plant for unintended effects.

[21] "Evaluation of Allergenicity of Genetically Modified Foods," Report of a Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology, January 22-25, 2001. See http://www.fao.org/es/ESN/food/pdf/allergygm.pdf.

Residues of plant-made animal drugs in animal tissues

(993-1001)

The guidance devotes just one sentence to the issue of plant-made animal drug residues in animal food tissues. Such residues could accumulate, for instance, by feeding corn that contains an animal vaccine to pigs. Rather than refer the matter to the Center for Veterinary Medicine for *ad hoc*, case-by-case consultation, this issue (like so many others raised but not discussed or regulated in this guidance) deserves thorough and systematic consideration. The FDA should also develop strict, detailed regulations for potential animal or human drug residues in animal food products arising from the feeding of biopharm crop materials (e.g. as fodder) or post-extraction byproducts.

Plant-produced pesticide residues in PMPs (951-56)

The FDA advises applicants who wish to stack biopharm crops with biopesticides such as Bt to contact the EPA "regarding the safety of the pesticide." Once again, as with chemical pesticides, it is somehow assumed that the EPA will be in a position to evaluate the novel risks posed by injection, ingestion or dermal application of biopesticide-laced biopharmaceuticals. This is simply not the case. In fact, the EPA has even failed to evaluate the current crop of plant-produced pesticides (the various Bt-derived insecticidal proteins expressed in corn & cotton) for allergenicity[22]. The EPA's failure to do this means that the FDA will have to conduct an independent assessment of the allergenicity and other possible health impacts of Bt endotoxin residues in biologics. Other prospective biopesticides may have other impacts for which testing will be required. For instance, a USDA scientist has proposed that biopharm crops be stacked with the biopesticide avidin, which not only kills a broad range of insects but also causes Vitamin B (biotin) deficiency in humans and animals that ingest it (FoE/GEFA Appendix 2).

Miscellaneous Comments

Tissue distribution of expression products (398-407)

The guidance requests information on expression levels in various tissues. It should also demand expression levels in these tissues over time throughout the growing season. Companies should also supply detailed data on variability in expression levels

[22] Freese, B. (2001), op. cit. (see footnote 16)

(in various tissues) from plant to plant, generation to generation and in plants of the same genetics grown in a wide range of environments, including extreme conditions (e.g. FoE/GEFA 4.6.2).

Environmental review (203-213)

Since APHIS has not conducted an environmental assessment (EA) of a biopharm field trial since 1998, there is little reason to fear "duplication" of environmental reviews among the various agencies. One EA per trial would represent a vast improvement over the current situation. Therefore, APHIS/BRS must marshal the personnel and resources needed to begin conducting EAs for all biopharm field trials and so justify the sentence: "APHIS/BRS will identify and evaluate the potential environmental effects posed by field growth of such plants." And future EAs should not be pro forma, boilerplate exercises, like most of the few prior environmental assessments conducted by APHIS, but rather real studies with real data (see FoE/GEFA 6.5).

Conclusion

Bureaucratic blinders

The following sentence reveals a fundamental weakness of the guidance document, which in fact is a fatal flaw in all aspects of GE crop "regulation":

> "This document only addresses FDA and USDA guidance; if you have questions regarding the use or safety of pesticides, you should contact EPA." (955-56)

This statement presumes that concerns raised by biopharming break neatly along bureaucratic fault lines. But of course they don't. As discussed above, EPA is competent to evaluate the risks of oral exposure to pesticides on food, ***not*** the risks of oral, dermal, intramuscular or intravenous doses of pesticide residues delivered together with another bioactive compound (the biopharmaceutical). FDA officials surely know this, but apparently cannot see beyond their bureaucratic blinders. Equally blind is FDA's refusal to concede the obvious need to examine – ***before any such field trials are permitted*** – the potential health effects resulting from biopharm crops contaminating food crops. But FDA refuses to consider this obvious matter not because it isn't worthy of consideration (it most certainly is), but merely because field trials of engineered plants are the USDA's responsibility – bureaucratic blinders once again. A third example is the gaping hole where there should be strict regulatory control of bioengineered plant-made industrial chemicals. EPA should be concerned

about environmental impacts, FDA about the potential health impacts (once again) of contaminated food crops, but instead the USDA is left to bungle along (understaffed and unduly influenced by the biotech industry) with next to no regulation of these novel crops. (In fact, industrial chemical crops are even grown under the USDA's weak notification system – 90% of field trial sites for "notifications" are not inspected at all by USDA inspectors.[23])

Economic self-interest ignored…

Perhaps the biggest failing of our government's "regulatory" system for all genetically engineered crops (including biopharm plants), however, is the failure to give any serious consideration to the economic impacts these crops are having and will continue to have on American farmers, the food industry, and indeed, the very reputation of America as a supplier of safe, healthy food. Government and industry are ***squandering*** this goodwill, this carefully cultivated and earned reputation, every day. Each new contamination episode, each new example of regulatory incompetence, makes government officials, food industry representatives and consumers in foreign nations that import our produce shake their heads in wonderment. "Why does America continue to ignore our elementary demands for safe food?" they wonder. "Why can't Americans seem to enact the most elementary regulations to keep drugs out of the food supply?"[24] Finally, they may decide to import their food from countries whose governments and growers are responsive to their needs. In fact, this process has already begun. Europe has virtually stopped importing corn from the U.S. due to the admixture of inadequately tested GE varieties. Brazil has increased its conventional soybean exports as Britain and other countries turn away from the U.S. market, which consists mainly of engineered soy, in search of non-engineered supplies.

In favor of fanatical "anti-regulation" ideology

The puzzling refusal of the U.S. government to regulate a field posing such patent risks to public health and potential for consumer backlash and massive export losses as drug-producing food crops is explained, at least in part, by a fanatical ideology that holds sway in certain influential government and industry circles. These "anti-government regulation" fanatics oppose, with truly religious fervor, any government initiative that in any way restricts the scope of private industry to do exactly as it pleases, even when such regulation would prove economically advantageous. Among anti-regulation

[23] Personal communication, Dr. James White, APHIS.
[24] The recent ProdiGene episodes in Iowa and Nebraska have reportedly been covered more heavily in European and Asian media than in the U.S.

cultists, government regulators are to be opposed, undermined, hamstrung or co-opted at every turn, in complete disregard of the facts of the case at hand.

Biopharming is an excellent proof of this thesis. Here's the situation in a nutshell:

1) **Contamination assured:** Experts agree that biopharm contamination is inevitable, especially with commercial-scale plantings. The promiscuous pollinator corn is by far the favorite biopharm host plant.

2) **Known health risks:** Several of the few PMPs that are known pose demonstrable health risks upon ingestion.

3) **Secrecy fuels legitimate suspicion:** The identities of most PMPs are kept hidden as company trade secrets. Could they pose still greater risks than those that are known?

4) **Government's "GMO force-feeding" policy harms American agriculture:** The U.S. government has thus far pursued a disastrous "force-feeding" policy with respect to GMOs that has resulted in substantial export losses. Bad as it has been, this policy will become still more disastrous in the age of open-air biopharming.

5) **Foreign grain traders adamantly opposed to new GMOs, especially biopharm:** It's not like we haven't been warned. Instead of threatening Europe with WTO challenges, maybe we should start listening to our foreign customers and giving them the products they want – food crops and products that are free of unregulated GMO content.

If one mark of fanaticism is to sacrifice one's rational self-interest for the sake of one's irrational beliefs, then the anti-regulation zealots can truly be said to be under the influence of a deeply irrational fanaticism. Until they are brought to their senses with respect to biopharming, American farmers, food companies and consumers will suffer from their delusions.