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Biopharming and Biosafety

Current Regulation of Biopharming: Is it Adequate?

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The use of genetic engineered plants to produce pharmaceuticals ("pharming") has the potential to provide tremendous consumer benefits, but if misused, also has the potential to harm consumers and the environment. Thus, a strong and transparent regulatory process is essential if our society is to reap the benefits from safe commercial applications of pharming.

The current federal regulatory system does not ensure thorough environmental assessments before the planting of pharma crops nor does it adequately prevent those crops from contaminating the food supply. It also does not adequately ensure that no human will be exposed to harmful pharmaceutical substances in food. Congress, the Food and Drug Administration ("FDA") and the United States Department of Agriculture ("USDA") need to set forth a rigorous and robust regulatory system that ensures both human and environmental safety from this technology. Until such a system is put in place, no pharma crops should be grown out in the open.[1]

I. The Current Regulatory System for Pharma Crops.

The USDA is the primary regulatory agency responsible for environmental concerns for GE crops while FDA will be responsible for their food safety.

A. USDA's Regulation of GE Crops.

Under the authority of the Plant Pest Act, USDA has established a regulatory system for genetically engineered plants that could become plant pests. Crops subject to those regulations include (1) any crop that is a listed plant pest, and (2) any crop that contains introduced DNA from a listed plant pest or an organism whose plant pest status is undetermined. For example, the regulations capture any GE crop that uses agrobactium DNA as part of its genetic construct to insert a new gene into a plant. The regulations do not include crops engineered using a gene gun, unless the inserted DNA comes from a listed plant pest or an organism whose plant pest status is undetermined.

Any plant covered by USDA's regulation must submit to one of three oversight processes before release into the environment. The first of those processes is a notification, in which the applicant provides USDA with details about its proposed release and USDA has thirty days to respond to the notification. USDA has established criteria to determine which products are eligible for the notification process and guidelines that must be met to minimize environmental effects from the release. Notification is currently used to regulate virtually all of the field tests for GE crops under USDA's jurisdiction and even for some crops that are grown commercially.

The second process is permitting, which requires a more detailed application and a longer review time at USDA before the release is authorized. GE plants that must be permitted (instead of a notification) include crops producing pharmaceuticals and those that could affect non-target organisms. Permitting is not used as commonly as the notification process, although hundreds of permits have been issued since USDA began regulating GE crops.

[1] Although pharma crops will produce drugs and vaccines, the drugs and vaccines produced will be regulated similarly to the conventionally produced products. Therefore, this presentation will not include a discussion of those regulatory issues.

The third process at USDA is a petition for non-regulated status. A petition is a request that USDA determine that there is no plant pest risk associated with the crop and that the crop no longer needs to be regulated. A petition for non-regulated status has been the primary pathway to commercialize GE crops. Before a petition is granted, USDA conducts an environmental assessment of the crop and seeks public input through a formal public comment period.

B. FDA's Regulation of GE Crops.

Currently, FDA does *not* formally approve any GE crops as safe to eat. Instead, FDA has determined that GE crops are similar to conventionally bred crops and should typically fall into the category of "generally recognized as safe" ("GRAS") foods. FDA's policy does allow a GE crop to be treated as a food additive requiring mandatory approval if that crop raises a food-safety concern. However, to date, FDA has not determined that any GE crop should be considered a food additive and it is unclear if any future crop will fall into that category. Both FDA and the biotechnology industry will strongly resist putting biotech foods through the food additive process, since that process is perceived as time-consuming and burdensome.

To oversee any potential food-safety concerns that might exist for a GE crop, FDA adopted a voluntary consultation process to review safety data provided by companies to ensure compliance with existing laws. In that process, the biotechnology company provides summary information about the food-safety of its product to FDA and FDA provides informal advice about the adequacy of the tests conducted by the company. In conducting its scientific safety assessment, the company provides information to show that its biotech variety is "substantially equivalent" or as safe as its conventionally bred counterpart. To date, almost all commercialized GE crops have proceeded through the voluntary consultation process before marketing.

II. Inadequacies with USDA's Current Regulatory System for Pharma Crops

There are numerous inadequacies with USDA's current regulation of GE pharma crops. First, the regulatory system only captures GE crops that could become plant pests, leaving a gap in USDA's authority so that some GE crops, such as those made with a gene gun and corn DNA, may not require even a notification before release into the environment. It is unclear whether there is scientific evidence that all pharma crops are potential plant pests and would be captured by USDA's regulations.

Second, for pharma crops, USDA's regulations do not require that a thorough environmental assessment occur prior to the plant's release into the environment. To date, the USDA has not conducted an Environmental Assessment under the National Environmental Policy Act for any pharma crop planted under a permit yet hundreds of permits have been issued for pharma plantings. In fact, crops released through either the notification or the permitting process almost never receive an individual environmental assessment, yet some of those crops might have significant environmental impacts. A recent National Research Council ("NRC") report determined that "With few exceptions, the environmental risks that might accompany future novel plants cannot be predicted. Therefore, they should be evaluated on a case-by-case basis." Yet, the notification and permitting process does not evaluate environmental risks on a case-by-case basis since no environmental assessment is conducted for most individual applications processed using those procedures.

Third, for those crops that do receive a thorough environmental assessment from USDA (consisting primarily of crops that seek nonregulated status), those environmental assessments are

inadequate. According to the NRC report: "Currently, APHIS environmental assessments focus on the simplest ecological scale.... APHIS should include any impact on regional farming practice or systems in its deregulation assessments." Thus, USDA's environmental assessments do not address all relevant environmental concerns.

Fourth, it is unclear whether USDA has the legal authority to adequately address environmental issues that arise in an environmental assessment. USDA has regulatory authority to address plant pest risks but does not have authority to prevent a crop's release if it may cause ecological harms unrelated to agriculture.

Fifth, USDA's regulations only provide for public participation and the opportunity to comment when a GE crop is petitioning for nonregulated status. USDA has stated, however, that no pharma crop will be granted nonregulated status. Although that position is appropriate, it means that there will be no public participation or opportunity to comment before the growing or commercialization of a pharma crop.

Sixth, the process at USDA involves no food-safety analysis of the crop before it is released into the environment. For open-pollinating crops such as corn, a release could result in the gene product entering the food chain. USDA's process makes no assessment whether that gene product will be harmful to humans if it does enter the food supply.

Finally, USDA permits for pharma crops require both (1) stringent confinement obligations to contain the gene and its product from escaping into the environment and (2) stringent segregation obligations to prevent contamination of the food supply. While the most recently announced permit conditions go farther than ever before at trying to prevent escape of the pharma crop, those permit conditions are not worth the paper they are written on if the industry does not comply with those conditions. The recent violations by Prodigene, as well as similar permit violations by Pioneer and DowAgrosciences for EPA issued permits for plants engineered to produce a pesticide, are evidence that the biotechnology industry cannot be trusted to abide by government-imposed planting obligations. With an industry that has a propensity to violate government-imposed permit obligations, USDA needs a vigorous enforcement and compliance program. USDA's enforcement program, however, does not sufficiently inspect field test site nor provide other mechanisms (such as third party independent auditing, farmer certification, and detailed documentation obligations) to ensure compliance with permit conditions.

III. Inadequacies in FDA's treatment of food safety issues surrounding pharma crops.

The Federal Food Drug and Cosmetic Act ("FFDCA") regulates anything that is intended to be used as food or feed. A pharmaceutical corn plant or a corn plant producing avidin, however, is not intended by the developer to be used as food or feed. Thus, those products are neither food additives, nor would they be subject to FDA's voluntary notification process (or FDA's proposed mandatory notification rule). FDA has limited authority over those products unless they show up in food. At that stage, FDA could consider foods containing the pharmaceutical drug or industrial chemical adulterated and remove them from the market. The burden would be on FDA, however, to prove they are adulterated.

Even if pharma crops were subject to FDA's current voluntary notification process, there are numerous problems with that policy. First, the consultation process is voluntary. There is no legal obligation that requires that companies provide a safety assessment to FDA and no

consequences to a company if they do not voluntarily consult. Second, the consultation process is developer-driven instead of FDA-driven. The biotechnology company decides what safety tests to conduct and what data to submit to FDA because the company's obligation is to satisfy itself that the product is safe rather than prove safety to FDA. The voluntary process provides FDA with limited ability to require specific tests or mandate specific data. Third, FDA's food-safety analysis is not comprehensive. FDA guidance states that the consultation process is "not a comprehensive scientific review of the data generated by the developer." Fourth, and most importantly, FDA does not determine if the product is safe. The voluntary consultation process culminates with FDA stating that it has "no further questions . . . at this time" regarding the food instead of a statement that the product is safe to eat.

The current system is not the best way to ensure a safe food supply, when contamination by non-food GE crops is inevitable. A possible solution to this problem would be for Congress to require a mandatory FDA approval process for all GE crops, both those intended for food use and pharma crops not intended for the food supply. Under that approval system, no GE crop grown in a food crop could be commercialized without a food-safety approval by FDA. For pharma crops to be commercialized, FDA would either need to approve the crop as safe to eat or set a safe tolerance for the non-food substance. Then, if that GE crop entered the food supply, eating the engineered substance would be safe as long as the substance was below the tolerance level. No consumers would need to fear that they were eating food with unsafe substances in it. In addition, the rigor of the food-safety assessment conducted by FDA could be proportionate to the physical and biological confinement of the crop. If the pharmaceutical plant was grown in a cave or a location far from other corn plants, only a limited food-safety assessment might be required because the likelihood of contamination would be extremely small. If the pharmaceutical plant was grown in Iowa, however, then a complete food-safety analysis might be warranted.

In the 106th Congress, Senator Richard Durbin from Illinois introduced the Genetically Engineered Foods Act (S. 3095). That bill would require all GE food crops to have a mandatory premarket approval before commercialization.

IV. The Key Components of a Rigorous and Robust System for Regulating the Human Health and Environmental Risks of Pharma Crops.

The recent incidents in Nebraska and Iowa involving pharma crops grown by Prodigene and the inadequacies identified above provide ample evidence of the need for USDA and FDA to use all their statutory authorities to regulate pharma crops. In particular, the regulatory system should do the following:

1. **Only allow the planting of pharma crops if the government issues a permit**. The regulatory system must put in place mandatory permitting requirements that must be complied with before the growing of any pharma crop. The permitting process should be transparent and allow for public participation before the issuance of the permit.

2. **Only issue a permit after a thorough environmental assessment of the potential risks from growing the pharma crop**. Before a permit is issued, the government should conduct a thorough environmental assessment of the potential effects of growing the pharma crop, including the effects from gene flow of the introduced gene and the effects of the transgenic protein on living species other than humans. The environmental assessment should comply with the National

Environmental Policy Act, although for each individual permit, there may or may not be the need for an Environmental Impact Statement or an Environmental Assessment.

3. **The permits issued should require strict biological and physical confinement measures**. All permits should contain enforceable conditions requiring state-of-the-art confinement procedures. Those mandatory permit conditions should include isolation distances, geographic restrictions (such as not growing GE corn in parts of the country where commodity corn is grown), physical barriers (such as fences or greenhouses), the use of distinguishable varieties of the crop, biological confinement (such as male sterility), and so forth. The permit should also require extensive segregation procedures that ensure that none of the harvested materials can co-mingle with crops destined for human or animal consumption. When using a food crop, the permit should have several redundant levels of confinement, even at the field trial level.

4. **The permits issued should require documentation of compliance with permit conditions**. All permits should contain education, certification, and documentation requirements. All persons working with pharma crops should be required to attend mandatory education seminars on the proper procedures to handle those crops and then obtain independent certification that they are qualified to participate in the handling of those crops. In addition, all permits should require the maintenance and then submittal to USDA of documentation verifying the compliance with permit obligations.

5. **The permits issued should require independent auditing of compliance with permit obligations**. As a condition of a permit, the developer should be required to hire a third-party independent auditor to oversee and assess compliance with permit obligations. That auditor should review documentation on compliance, regularly inspect the growing of the crop, and interview employees and contractors working with the crop. They should provide regular reports to FDA and USDA identifying all compliance issues.

6. **USDA and FDA should regularly inspect the production of the pharmaceutical in the plant**. As part of its regulation of pharma crops, both USDA and FDA should conduct regular, unannounced inspections of all facilities involved in the production of the pharmaceutical, from the laboratory to the farm to the manufacturing plants. Those inspections should occur after the crops have been harvested to prevent volunteer plants in future seasons. In addition, USDA and FDA should also inspect neighboring fields and crops to confirm that containment has been achieved.

7. **For pharma crops grown in food crops, there should be a mandatory pre-market food-safety approval process by FDA's Center for Food Safety and Applied Nutrition**. Although confinement measures need to be strictly adhered to, they will never result in 100% containment over

the long term. Thus, before any pharmaceutical is grown commercially in a food crop, FDA should conduct a thorough food-safety analysis to ensure that human exposure to the transgenic crop in the food supply will not result in any health risks. If additional legal authority is needed to implement this requirement, FDA and USDA should ask Congress to provide such authority.

V. Conclusion

Although agricultural biotechnology may allow us a new method to produce useful medical products, the current federal regulatory structure is not up to the task of safeguarding humans and the environment from that technology. With new legal authority and better regulations, a strong, but not stifling, system can be established that independently reviews and approves products that are safe for consumers and the environment. Such a system is essential if consumers are to have confidence in biotechnology and accept pharmaceuticals produced through agricultural biotechnology.