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4 February 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Dear Sir or Madam:

In response to the recent draft entitled, "Guidance for Industry: Drugs, Biologics, and Medical Devices Derived From Bioengineered Plants for Use in Humans and Animals," Docket No. 02D-0324, I support the FDA and USDA's guidelines to ensure the safe production of plant-based pharmaceuticals. However, I also have concerns that the guidelines are not sufficiently rigorous.

I have been working with plant-based pharmaceuticals for more than four years in both the private and public sectors. While in the private sector, I was a biotechnology regulatory manager and risk assessor for plant-based animal biologics. Additionally, I am an expert in environmental risk assessment and have been working on assessments of pesticides and biotechnology crops for more than six years. I currently am the leader of the Agricultural and Biological Risk Assessment program at Montana State University, a relatively new research, teaching, and outreach program dedicated to assessing and communicating risks from agricultural technologies. A significant portion of my efforts are dedicated to promulgating best approaches for assessing risks for plant-based pharmaceuticals.

Although plant-based pharmaceutical technology represents a great opportunity with tremendous potential, I also recognize that the potential technical, financial, and perceived risks from this technology could, if improperly regulated, limit its great potential.

To fully appreciate this issue and to design guidelines that are meaningful and sufficiently rigorous, it is crucial to recognize that there are two definitions of risk: (1) risk as a function of hazard and exposure, and (2) risk as a function of perception.

From a regulatory perspective, regulation of an activity or technology should be commensurate with risk. Therefore, assessments of risk (which include considerations of both hazard and exposure) are used to guide appropriate, cost effective, regulations. The paradigm of risk assessment should be used to

evaluate risks associated with plant-based pharmaceuticals. Technologies are based on science; therefore, science-based frameworks must be used to assess risk from those technologies. To that end, the risk assessment paradigm is sufficiently robust to assess risk from plant-based pharmaceuticals. Although not without limitations, risk assessment is currently being used effectively by all of the U.S. regulatory agencies that are overseeing plants produced using recombinant DNA technology. To increase public trust in plant-based pharmaceuticals, the regulatory agencies involved should employ the risk assessment paradigm and communicate transparently the procedures, risks, and decisions to the public.

However, truly new technologies often necessitate regulation in excess of purely technical risks. In these cases, public perceptions of risk also should be used and weighted accordingly to promulgate regulations. This position fits well within the paradigm of risk analysis, which is the dominant policy-making and implementation tool for environmental issues within the U.S. federal government.

Plant-based pharmaceutical technology represents a truly new technology. Consequently, public perceptions must be taken into account in addition to the conventional risk assessments that will occur. To that end, regulation of plant-based pharmaceuticals and crops should follow a path similar to the first recombinant DNA pharmaceuticals and biologics. Those processes and products were initially regulated in excess of their technical risk profile because of the newness of biotechnology and the need to develop public trust. This approach is even more salient for plant-based pharmaceuticals because non-food proteins will be produced in food crops. Further, the plants will be produced in the open environment, a unique aspect of pharmaceutical manufacturing. In a field environment, containment is possible and amenable to strict regulation, but containment is inherently less certain compared to traditional pharmaceutical manufacturing processes.

The above considerations must be used to develop the FDA/USDA guidance. However, the current FDA/USDA guidance is not sufficiently rigorous with regard to perceptions of risk from this important technology. I will detail the inadequacies of the guidance below.

Lines 136-138. The definition of a "bioengineered pharmaceutical plant" is poor and may lead to confusion by the public. The recombinant DNA technology does **NOT** express a gene encoding a biological or drug **product**. The definition (and regulation) of a product is quite different from the protein expressed in the plant. Production of pharmaceutical proteins in plants represents a novel step in the production of pharmaceuticals and biologics. The plant is not the final pharmaceutical product, just as microbial or yeast pharmaceutical production systems do not represent the final product. Rather, the plant represents just one step in a complex, multi-step pharmaceutical production process. There is no such thing as a "plant-made pharmaceutical." I am surprised to see this confusion of terms in a regulatory guidance document. I suggest the term "plant-based pharmaceutical," which indicates that the plant forms the manufacturing basis for the eventual production of the drug or biologic.

Lines 269-274. The recommendations should be changed to requirements. In other words, measures MUST be in place to ensure that there is not inadvertent mixing of... Also, tests that can detect the target gene and expressed protein MUST be available.

Lines 416-418. Change "confinement measures that may be needed to control the spread of bioengineered pharmaceutical plants" to "confinement measures that must be implemented to control..."

Lines 431-433. The sentence, "Growing plants in such an enclosed building does not require a USDA/APHIS/BRS permit, however, the importation or interstate movement of bioengineered pharmaceutical plants would require a permit (7 CFR 340.4)" is not acceptable policy. Under this scenario, without the need for a permit, it is possible to grow these crops in a greenhouse immediately adjacent to a field of crops of the same species meant for food use. For example, if the initial maize transformants are produced in Texas and the resulting progeny are grown in a greenhouse in Texas, there is no permit that will be required. This clearly is unacceptable because without a permit for the greenhouse production, there is no way to ensure that the greenhouse has adequate confinement measures in place.

Lines 492-494. Change "measures should be in place..." to "measures must be in place..."

To further bolster public trust in this technology, I recommend the following:

1. Crops producing non-food proteins for pharmaceutical or biologics uses should **NEVER** be de-regulated. Important regulatory processes for pharmaceuticals (such as the required plan of production) will be compromised if these crops are de-regulated.
2. The Agencies **MUST** require dedicated agricultural equipment during all stages in the pharmaceutical or biologics manufacturing process.
3. The Agencies **MUST** require processing of seeds, grains, and other plant structures in facilities clearly outside the commodity grain channel. Commercial mills should never be used to process these materials.
4. Finally, there **MUST** be equivalent regulation for all food crops which are not intended to be used for food or feed. This includes not only plant-based pharmaceuticals and biologics, but also plant-based industrial products.

In summary, I am a strong advocate of the risk assessment paradigm to assist our democratic society in making decisions about how to manage any technology. Indeed, I have devoted my career to the risk assessment paradigm. Science-based risk assessment must be used in a case-by-case fashion to evaluate and communicate risks posed by plant-based pharmaceuticals. Further, this process must be as transparent as possible.

Despite my commitment to risk assessment, I also recognize that new technologies often require regulations in excess of their technical risks. I believe to ensure the success of this promising technology, we must consider public perceptions carefully and implement appropriate regulatory policy. To

that end, I support regulation of this technology which may be more rigorous than what a risk assessor may recommend based solely on a science-based assessment of risk. Regulations in a democratic society rarely are made based upon risk assessment alone. Indeed, the paradigm of risk analysis can be defined as a rational framework whereby the knowledge-based description of risk (a science driven process) is integrated with social, cultural, economic, and political considerations to manage and communicate risk in policy decisions and implementation. Consequently, the paradigm of risk analysis, where risk assessment resides, is fully capable of incorporating public perceptions into the decision-making process.

Plant-based pharmaceutical technology represents a great opportunity with tremendous potential to improve human and animal health. I strongly encourage FDA and USDA to regulate this technology so that its full benefits can be realized.

Sincerely,

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