Consumer Policy Institute
Consumers Union

Comments of Consumers Union on Docket No. 02D-0324: Draft "Guidance for Industry: Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals

Overview

Consumers Union* welcomes the opportunity to comment on the Food and Drug Administration's (FDA's) and U.S. Department of Agriculture (USDA) proposed draft guidance on the growing of plants that have been genetically engineered to produce drugs. We support FDA's goal of insuring that such plants do not get into human food or animal feed. However we do not believe that the industry guidance will achieve that important goal. In fact, for the reasons we outline, we think that even if industry follows this guidance, but takes no other measures, significant contamination of the food supply is inevitable.

We believe FDA should establish a zero tolerance for drugs, biologics and medical devices in food and feed. To achieve this, FDA/USDA guidance should indicate that drugs, biologics and medical devices should not be genetically engineered into food crops. Rather, to achieve the potential benefits of using this technology FDA should guide companies to investigate engineering of such substances into non-food crops, if they can be grown indoors under controlled conditions.

FDA Should Set a Zero Tolerance for Drugs in Food

We strongly agree with FDA's statement in section II. A. that, in regard to using "a food crop species engineered to produce non-food materials" that "the presence of any such material [drug, biologic or medical device] in food or feed could render such products adulterated under the FD&C (12 U.S.C. 342)." We believe that any drug, biologic or medical device produced in genetically engineered food crop species should be considered an adulterant if present in food or feed at any level. Drugs, biologics and medical devices are highly regulated products that FDA does not allow on the market without a prior safety

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review. They are designed to be biologically active substances. In part because of risks associated with these substances, consumers are not allowed to purchase prescription drugs without a physician sanctioning such use and indicating the dosage and time period of administration, and manufacturers are tightly regulated as to production practices.

Consumers do not expect to have drugs, biologics or medical devices in their food, and such presence would raise complex and important safety issues. To take just one example, few drug safety evaluations conduct testing to evaluate the possible effects of consumption of low levels of the drug continuously over a lifetime, beginning in early childhood or even infancy. Nor do such evaluations examine the synergistic or cross-reactive effects of consumption of the hundreds of drugs which eventually could be produced in plants. In fact, it is not possible to do a scientific credible risk assessment of these potential public health hazards, given currently available data or any reasonable scenario for near-term research. In the face of such great scientific uncertainty, the FDA should set a zero tolerance for such "non-food (or non-feed) material" in food.

FDA Should Not Allow Food Crops Species as Source Plants

The FDA states in II.A. that a concern that must be addressed is "the measures to ensure that non-food (or non-feed) material will not get into food or feed." We agree with that goal. However, we believe that the present guidance will not achieve that goal. Indeed, for the reasons discussed below, we believe that the measures described in this guidance are so minimal and ineffectual, that even if they were followed by industry, and no other measures were taken, it is inevitable that drugs and biologics would get into food or feed. The measures described in the FDA/USDA proposal specifically do not address prevention of additional incidents like those that occurred in 2002 involving Prodigene field trials.

In our view, the only way "to ensure that non-food (or non-feed) material will not get into food or feed" is to indicate in the guidance that companies should not use of food crop species as a source of "the desired regulated product." If the agency allows companies to use a food crop species as a source—whether grown outdoors or indoors in a greenhouse—contamination of food and feed will be inevitable, through biological means and/or human error. Biological means of contamination include gene flow—via pollen and seeds—which can occur through vectors ranging from bees and wind to tornadoes. Human error includes many things, such as the accidental mixing of seeds, or insufficient diligence in removing volunteers in the year(s) subsequent to the planting of pharmaceutical crops. Effects of possible deliberate sabotage—whether terrorist or vandalism—can also not be discounted. Gene flow is an

especially serious concern, given that some two-thirds of the field trials to date of pharmaceutical crops have involved the use of corn, a wind-pollinated crop, as the source crop. Corn is planted on tens of millions of acres.

The examples of the ProdiGene contamination events last fall suggest that containment is virtually impossible. Last November, the USDA and FDA made public the discovery of problems of contamination of food crops—soybeans and corn—from two ProdiGene field trials, one in Iowa and one in Nebraska. According to ProdiGene, both trials involved corn engineered to produce TGEV, a pig vaccine (Gillis, 2002a). The FDA, however, put out a press statement saying that in the Nebraska case, an unapproved human drug had been engineered into the corn: "The pharmaceutical material being produced in the corn plants was being studied under an Investigational New Drug (IND) application" (FDA, 2002). Regardless of which is accurate, the contamination is still a recognized fact. With more than 300 experiments already, and untold more planned, plus likely commercial scale planting of some, if this technology goes ahead on current track our food will be massively and most likely irreversibly contaminated.

Detailed Comments

III. Environmental Considerations
C. Confinement measures
1. General Considerations

The agency suggests, that when developing a bioengineered pharmaceutical plant, that companies "should implement procedures to ensure that such a plant line is used only for its intended purpose as a source material for a regulated product" and then suggests that the company keep detailed records "documenting the handling and transfer of such materials." But detailed records will not ensure that no contamination of food or feed will occur. Human error can occur. Records can be incomplete, or even falsified. Further, paper records can be lost and computer records can be accidentally erased. In addition, fires can destroy such records, particularly if multiple back-up copies are not kept in several locations.

The agency also suggests that companies "should consider the use of strategies—[such as using genetic markers that alter the physical appearance of the plant, e.g. novel color or leaf pattern]—that allow the bioengineered pharmaceutical plant line to be readily distinguished from its food or feed counterpart" or "strategies to reduce the likelihood of unintended exposure to the regulated product by" restricting where (via the use of tissue-specific promoters) or under what conditions (via use of inducible promoters) the product will be expressed. We note that while such suggested mitigation

concepts are good ones, none of them are foolproof. Such measures help clarify that contamination has occurred. However, it may not prevent it in the first place. Also, since such measures are voluntary, there is no assurance that they will be used. Indeed, companies have indicated a reluctance to alter color or leaf pattern because they believe that if the product is readily identifiable, it might become the target of vandalism. In fact, we have seen no evidence to date that *any* of these measures have been utilized in the hundreds of field tests done so far.

FDA further suggests planting outcrossing plants "only in regions of the country where little or none of its food/feed counterparts are grown." We note that so far this is not industry practice, as evidenced by the two examples of contamination of soybean crops with volunteer pharmaceutical producing corn that took place last fall. In these two ProdiGene examples, the pharmaceutical producing corn had been grown in Nebraska and Iowa, both of which are part of the corn belt. Further, this advice has already apparently been rejected by industry. A few weeks before the ProdiGene contamination stories appeared in the press, BIO (Biotechnology Industry Organization) announced a voluntary moratorium on planting pharmaceutical corn (the majority of field tests have used corn as the source plant) in the corn belt (Gillis, 2002b; Brasher, 2002). This would have been a positive, although limited step-- it should be pointed out that there are some 20 million acres of corn grown outside the corn belt. However this policy was short-lived. In early December, BIO sent a letter to Senator Charles Grassley (R-Iowa) in which they rescinded this voluntary moratorium and stated, instead, that they would defer to whatever future guidance or regulations were proposed by FDA and USDA (DTN, 2002).

In addition, there is the potential for pollen flow from such pharmaceutical plants (e.g. corn) to non-pharmaceutical plants during the seed production stage; this has been shown to occur with StarLink corn (USDA, 2001). Even if one could find regions of the U.S. where little or no food/feed counterparts are grown (a doubtful proposition, particularly for corn plants, which account for the bulk of the field trials), the possibility exists that bags of such pharmaceutical seeds might be mis-labeled or inadvertantly mixed with non-pharmaceutical seeds, and then unknowingly planted.

The agency also suggests that "[M]easures should be in place to ensure that there is no inadvertent mixing of the bioengineered pharmaceutical plant with plant material intended for food or feed (including inadvertent mixing with seeds for food or feed crops)" and basically suggests companies use a HACCP approach to "determine where in the process inadvertent mixing could occur and establish appropriate control measures." Such a HACCP system is currently being used to control microbial contamination in meat production facilities and a recent GAO report has pointed out numerous short-comings in such a system

(GAO, 2002a). Since HACCP has only made modest progress in controlling microbial contamination of meat products in slaughterhouses and other processing facilities, it is difficult to believe that a HACCP system would be foolproof in preventing contamination of food and/or feed with materials from bioengineered pharmaceutical plants.

The FDA has also "strongly suggested" development of tests "that can detect the presence of the target gene and the protein product in the raw agricultural commodity." We believe that such tests should be required as a precondition to the use of any plant species as the source of the pharmaceutical product. However, having such tests available won't prevent contamination—it will simply allow the existence of contamination to be detected. Since development of such tests is optional—neither FDA nor USDA have the regulatory authority to require them—there is no assurance that such a system would be able to reliably detect a contamination event.

The details of the two ProdiGene examples, from Nebraska and Iowa, show that FDA and USDA cannot rely on industry self-policing in this area. In the Iowa case, which was discovered in September, 2002, ProdiGene did not come forward and tell the USDA that volunteer pharmaceutical corn plants existed in the field of soybeans planted in 2002. (In 2001, this field had been planted to an engineered pharmaceutical corn.) A USDA inspector visiting the Iowa location in September found 20 volunteer corn plants standing in the soybean field in addition to a pile of rogue corn plants at the side of the field (NGO mtg. with APHIS/BRS staff, Jan. 14, 2003). The plants had flowered, so that pollen could have contaminated nearby corn fields. USDA acted in a conservative manner and ordered some 155 acres of corn to be destroyed (Gillis, 2002c). USDA did this, in part, because they did not have the ability to test the neighboring corn for the presence of the pharmaceutical transgene.

In part because ProdiGene had not notified USDA of the volunteer pharmaceutical corn plants in Iowa, USDA decided to check all the other ProdiGene field sites (NGO meeting with APHIS/BRS staff, 1/14/'03). In early October, 2002, a USDA inspector found 211 pharmaceutical corn volunteers—some of which had flowered—in a Nebraska soybean field that had been planted in 2001 to pharmaceutical corn (NGO meeting with APHIS/BRS staff, Jan. 14, 2003). Again, ProdiGene had not previously notified the USDA about the presence of such volunteers; this constituted a violation of their permit. The USDA inspector told the company to destroy the volunteers and the company supposedly relayed this message to their consultant and to the contract farmer, but the action wasn't fully completed (Ibid). Indeed, some of the soy had already been harvested and mixed with a silo of soybeans, thereby potentially contaminating the whole silo. USDA responded by quarantining some 500,000 bushels of soybean (Brasher, 2002). Blame was variously placed at the feet of

ProdiGene, the contract farmer, and consultants. The lesson for the FDA guidance must be that human error, failures of judgment, and lack of accountability must be expected and guarded against.

2. *Control of Seed Stocks*

The agency recommends that the companies should "maintain careful control over the inventory and disposition of viable seeds to preclude the possibility that such seeds will be used to produce material that could be used for food or feed production" and further suggests prominently labeling such seed stocks. However, we have already seen that the use of labels is unlikely to ensure that seed for drug production does not contaminate seed designed to be grown for food or feed.

Experiences with StarLink corn and with the FDA bovine spongiform encephalopathy feed rule demonstrate the shortcomings of labels as a means of preventing contamination. The Environmental Protection Agency (EPA), as part of the approval process for StarLink corn, allowed the corn on the market but stated that it could be used only for animal feed purposes. Seed bags were supposed to be clearly labeled that StarLink could not be used for human food. In addition, the farmers were supposed to be required to sign a contract that stipulated a number of items—such as not growing StarLink within 660 meters of corn destined for use as human food, use of buffer rows of corn, etc. These measures were supposed to ensure that none of the Starlink corn got into the human food chain. However, many farmers now claim that they never saw the contracts that they were supposed to have signed. In addition, the labeling on the many bags of seed did not explicitly say that it could not be used as human food (Ryberg, 2000). Despite EPA's labeling requirements and other precautions, the human food chain was contaminated with StarLink corn. In the end, companies had to spend over $1 billion recalling all the products that had been contaminated. Contaminated exports were identified as late as December, 2002 (Fabi, 2002). Even a significant percentage of corn seed was contaminated with genetic material from StarLink, demonstrating that gene flow had occurred (USDA, 2001).

To take another labeling example, in 1997, the FDA promulgated a feed rule designed to minimize the chance that mad cow disease would become a problem in the U.S. Part of the feed rule required that any animal feed that contained ruminant or other banned proteins be labeled "do not feed to cattle and other ruminants." A Government Accounting Office (GAO) study published in September 2000 found that 28 percent of all the facilities that handled ruminant meat and bone meal failed to put such a label on their product (GAO, 2000); a follow-up study found that labeling problems still persisted (GAO, 2002b). We have no confidence that the biotechnology industry, facing

voluntary guidance, will succeed when other industries, under a regulatory mandate, have massively failed.

3. Field-grown plants

On the question of field-grown plants, USDA and FDA "recommend that you [the company] consider the use of perimeter fencing to help exclude wildlife and escaped livestock." Such a step, while perhaps marginally useful, will certainly not stop birds and insects from entering the fields and consuming or transporting seeds and/or pollen out of the field site, potentially contaminating food crops. Such animals, in addition, could be affected by the pharmaceutical products themselves, including beneficial species. Furthermore, a fence is useless against major acts of nature such as flooding and tornados. The floods that ravaged the mid-west in the late 1990s destroyed some test plots (NGO meeting with APHIS/BRS staff, 1/14/03). There was also at least one incident where a tornado destroyed a plot of tobacco containing transgenic proteins in Kentucky in the mid-1990s. This Kentucky case, which involved the transgenic tobacco mosaic virus (TMV), could have resulted in the spread of the virus. Although a tornado would destroy the experimental tobacco plants, TMV can be transmitted by direct contact to other solanaceous plants such as tomatoes and potatoes. Thus, a piece of tobacco infected with transgenic TMV that floated back down to earth after the tornado could infect a tomato plant if the tobacco fragment touched a tomato plant. Such acts of nature could easily serve to spread the pharmaceutical plants far beyond the bounds of the test plots.

4. Control of harvest material

The agency notes that APHIS "requires [that] [D]uring transport, containers of harvested material should carry a label that clearly indicates that the material, including but not limited to seeds, leaves, roots, and stems is not to be used for food or feed." Such labeling cannot be relied upon, as the case of StarLink, as discussed above, clearly demonstrates.

5. Control at Processing Facilities

The agency proposes potentially allowing pharmaceutical plants to be processed at facilities that produce food or feed. The guidance states that "[S]ource plant materials should not be processed at facilities that are also used for the production of food or feed, such as grain mills, without prior consultation with USDA/APHIS/BRS or FDA." We strongly disagree and believe that under no circumstances should engineered pharmaceutical plants be processed at facilities that also produce food or feed. Such processing would inevitably result in cross-contamination of food or feed products. To achieve zero tolerance, pharmaceutical crops should have a completely separate production chain.

6. *Control of Waste Material*

This section would allow, under certain circumstances, that process waste or residual source plant material could potentially be used in human or animal food: "In process wastes . . . , rejected in-process material, and residual source plant material from the purification process . . . should be disposed in a manner to ensure that the material will not enter the human or animal food chain *unless you have specifically consulted with FDA for the use of this material in food or feed products*" italics added. We strongly disagree with the idea that process wastes could be fed to food animals. We urge that for safety reasons, this be prohibited, since just as in terms of human safety, the risk assessment process would be impossible to execute in a scientifically sound manner.

Conclusion

In sum, we think that the confinement measures laid out in the Guidance, and listed above, will not guarantee that the goal of zero tolerance—a proper goal in our view—will be reached. A zero tolerance is needed because acceptable risk levels simply cannot be established based on current scientific knowledge. We believe that the only way to achieve the goal of zero tolerance is to ban the use of food crop species as a source plant material for pharmaceutical production. This means that food crop plants should not be permitted to be engineered for pharmaceutical production, regardless of whether they are grown outdoors or indoors. Even if the crops were grown indoors, there is the strong possibility of a mistake which could mix up the seeds of food crop engineered with pharmaceuticals with seeds of the same food crop destined for human consumption, or a natural disaster, which would disseminate pollen.

As for non-food (or non-feed) plants engineered to produce pharmaceuticals and grown outdoors, while there would be no potential contamination of human or animal foods or feeds, we believe it is vitally important to consider the effects on non-target organisms and the environment, such as soil flora and fauna. Since pharmaceutical products, by their very nature, are designed to be biologically active, the risks need thorough and cautious assessment. Currently, the data are not available to conduct a valid assessment.

Consider the following hypothetical examples. One could engineer non-food or non-feed plants to produce the botulinum toxin that is used in BoTox for cosmetic purposes. The bacteria that produces botulinum only produces it under anaerobic conditions. If the gene were placed in a non-food plant and grown widely outdoors, the environment could be contaminated and numerous non-target organisms such as mammals could be adversely affected. There is also the example of various animal protein hormones such as bovine or ovine growth

hormone, or epidermal growth factor. Such compounds, if grown in non-food plants, could have effects on wild bovids or various wild ruminants such as deer, elk, bison, etc. if they accidentally consumed plants that contain these substances (The plant matrix may ensure that these protein hormones partially or fully survive digestion and could have effects). There is also the example of powerful antibiotics, such as chloramphenicol or others. While there are bacteria in the environment that may produce such antibiotics, engineering the antibiotic in a non-food plant and growing in on a large scale could potentially lead to far far higher levels in the environment than occur naturally. Indeed, all the above biologically active compounds could have negative effects on the environment and on non-target animals.

Thus, we believe production of pharmaceuticals in non-food or non-feed plants should not be permitted outdoors. However, we also recognize that there may be advantages to producing pharmaceuticals in plants. We therefore believe that companies should explore the use of non-food and non-feed plants in controlled conditions indoors—such as in greenhouses or phytotrons.

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