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# Regulating Transgenic “Pharm” Plants: Pre-Commercialization Review and Post-Commercialization Monitoring

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## **Abstract**

*This manuscript presents an analysis of the regulation of transgenic plants that are engineered to express pharmaceutical or industrial products (referred to throughout as “pharm” plants). Pharm plants promise to facilitate the inexpensive production of a variety of specialty products. However, critics have questioned the adequacy of regulatory measures that are intended to safeguard the food supply and the environment. Many pharm plants express unusual products that have not previously entered the food supply, and in many instances the products are intended to have pharmacological effects in humans. The commingling of such plants with food crops could have adverse effects on the safety of the food supply. The current regulatory system relies on processes that are intended to contain the pharm plants, preventing the commingling of pharm plants or their transgenes with food crops or wild plants. A review of the literature on transgene spread, much of it garnered from field experience with the widely commercialized transgenic herbicide- and pest-resistant plants, illustrates the inadequacy of such containment methods. More effective, self-perpetuating biological containment systems exist, but at present there is no effort to gather the environmental and food safety information that would provide a rational basis for determining the appropriate level of containment. By requiring a pre-commercialization review of the environmental and food safety hazards for each new pharm plant, regulatory agencies would be able to set containment measures according to cost-benefit principles. A pre-market review system will provide sound risk predictions for food toxicity issues, but scientists’ abilities to predict environmental risks and food allergy risks are limited. A post-commercialization monitoring system should be used to facilitate the detection of and response to unforeseen adverse events. By combining greater pre-commercialization review and post-commercialization monitoring, regulatory agencies can achieve a greater degree of certainty and credibility.*

## Introduction and Summary

Beginning with the open field growth of the Flavr Savr<sup>TM</sup> tomato in 1992, the agricultural biotechnology industry has engaged the world food supply in a grand experiment with transgenic plants.<sup>1</sup> The Flavr Savr tomato never took hold with consumers, but a host of engineered grain crops became available in the mid-1990s. The widely adopted Roundup Ready<sup>TM</sup> brand of soybeans contains a transgene that confers resistance to the herbicide glyphosate. Pest-resistant varieties of corn contain a transgene for a protein toxin of the bacterium *Bacillus thuringensis* (“Bt” toxin). Bt toxin conferred resistance to the European corn borer. These grain crops were quickly followed by pest-resistant and herbicide-resistant cotton and canola and pest-resistant papaya varieties.

This group of “first generation” transgenic plants has been a commercial success. By 2001 over 60% of soybean acres were planted with herbicide resistant soybeans, over 50% of cotton acres were planted with herbicide tolerant varieties and about 20% of corn acres were planted with pest-resistant varieties.<sup>2</sup> These crops are also credited with a variety of economic, environmental and agronomic benefits. The cultivation of Roundup Ready soybeans has led to increased use of no-till or conservation tillage techniques that reduce erosion and topsoil loss.<sup>3</sup> By increasing the use of glyphosate, a relatively non-toxic and biodegradable herbicide, Roundup Ready crops have decreased the use of more dangerous herbicides.<sup>4</sup> Glyphosate resistant canola, an oilseed crop also known as rapeseed, has been widely planted in the U.S. and Canada. A report from the Canola Council of Canada found, “Clearly, the majority of growers surveyed believed that there

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<sup>1</sup>Jorge Fernandez-Cornejo and William D. McBride, *Adoption of Bioengineered Crops*, Agricultural Economic Report No. 810, May, 2002.

<sup>2</sup>*Id.* at 1.

<sup>3</sup>*Id.* at 28.

<sup>4</sup>*Id.*

are significant advantages to transgenic canola. Participants in the survey and in the case studies stated that their primary reason for adopting transgenic canola were not economic, but agronomic. The transgenic system is simple, the weed control is early and effective, and the system fits well into a reduced or no-till operation.”<sup>5</sup>

At the same time, transgenic plants have encountered strong consumer resistance, particularly in Europe and Asia and in the American organic food market. Scientists and advocacy groups have expressed concerns about possible health and environmental safety risks that might be impossible to reverse, particularly once transgenic plants are spread throughout the agricultural system,.

For better or worse, the first generation of transgenic plants appears to be inextricably lodged in the North American food supply.<sup>6</sup> A new, “second generation” of transgenic plants is under development, and some such plants are now cultivated in open field trials. Many of these second generation plants are the first efforts of a new industry: instead of being grown for food, these plants have been engineered to produce industrial or pharmaceutical products, including specialty oils, plastics, industrial enzymes, pharmaceutically active proteins and vaccines.<sup>7</sup> The plants are used as a kind of solar-powered manufacturing facility. This technology has been dubbed “pharming”, and the advent of “pharm” plants has provided fresh vigor to the debate surrounding transgenic plants.

Pharm plants hold the potential to revolutionize the manufacture of many raw materials and chemicals.

Some experts have predicted that the field of vaccine development will be transformed by vaccine production

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<sup>5</sup>*An Agronomic and Economic Assessment of Transgenic Canola* Prepared for the Canola Council of Canada Prepared by: Serecon Management Consulting Inc. and Koch Paul Associates January 2001. Accessed at [http://www.canola-council.org/production/gmo\\_toc.html](http://www.canola-council.org/production/gmo_toc.html).

<sup>6</sup>David Barboza, *As Biotech Crops Multiply, Consumers Get Little Choice*, THE NEW YORK TIMES, June 10, 2001.

<sup>7</sup>National Research Council, Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation, National Academy Press, 2002 at 228.

in transgenic crops.<sup>8</sup> Additionally, industry executives are hopeful that pharm plants will lower the cost of production for therapeutically active proteins and provide nearly limitless manufacturing capacity.<sup>9</sup> The biotechnology industry is generating a host of highly selective protein-based drugs for the treatment of human diseases. Protein drugs are presently manufactured in large fermentation vats containing mammalian cells that are engineered to produce the desired protein.<sup>10</sup> Fermentation is expensive and the worldwide capacity for manufacturing protein-based drugs is expected to lag behind the demand for such drugs. Antibodies are a commonly used type of protein drug. Industry estimates suggest that the cost of antibodies produced in corn will be roughly one-eighth the cost of antibodies produced in bioreactors.<sup>11</sup> It is possible that pharm plants would decrease the cost of this quickly growing category of pharmaceutical agents.

At the same time, pharm plants pose substantial threats to the food supply. The first generation of transgenic plants, characterized by herbicide and pest-resistance traits, have not caused any clear damage to human health or the environment.<sup>12</sup> It is an entirely different matter to consider the human health hazards presented by a food plant, such as corn, engineered to express proteins that have a pharmaceutical effect on humans. Any commingling of corn containing pharmaceutical proteins with conventional food corn would contaminate the food supply. This prospect is at best unappetizing and at worst a health hazard. To prevent such an event, regulatory agencies require a series of cultivation techniques intended to decrease the risk of commingling between the pharm and the farm. The experience with the first generation plants does not instill confidence in the ability of governmental or private controls to keep the pharm plants off the food farm. If the plants

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<sup>8</sup>*Pharming the Field: A look at the benefits and risks of Bioengineering Plants*, Conference sponsored by the Pew Initiative on Food and Biotechnology, the U.S. Food and Drug Administration and Cooperative State Research, Education and Extension Service of the U.S. Department of Agriculture, July 2002.

<sup>9</sup>Pharming, *supra* note 8.

<sup>10</sup>NRC 2002, *supra* note 8, at 228.

<sup>11</sup>*Id.*

<sup>12</sup>Gregory Jaffe, *Food Biotechnology: A Legal Perspective: Remarks on Regulating Genetically Modified Foods in the United States*, 10 Rich. J.L. & Tech. 8, 2004.

are not properly regulated, escapes and mishaps may stir sufficient public resentment to doom or delay the adoption of this promising technology.

This manuscript focuses on the regulation of pharm plants, with a particular emphasis on the lessons learned from regulatory successes and failures with the first generation transgenic plants.

Part I is a review of the current regulatory system for pharm plants. Governmental agencies manage the risks associated with pharm plants by relying almost exclusively on physical containment. Presumably, if pharm plants cannot escape confinement, they will pose no risks to the food supply or the environment. However, an analysis in Part II of experiences with the first generation of transgenic plants demonstrates the overwhelming difficulty of containment. Transgenes have moved from crop to crop, apparently at will, and the true extent of the spread of transgenic material is still unfolding. Even the most stringent efforts to contain field grown plants have come perilously close to failure. Part II concludes with an evaluation of alternative containment options. A range of containment technologies are available, but increasing certainty in containment comes at a cost. Information regarding environmental and health risks for each individual type of pharm plant could form a rational basis for selecting an appropriate containment technology, and yet the present regulatory system does not elicit such information. In Part III, I evaluate the possibility of using a pre-commercialization review process to assess the risks posed by pharm plants to the environment and the food supply. Although food toxicity can be evaluated quite well, the possibility of unforeseen adverse events remain, particularly with respect to food allergies and environmental effects. Part IV presents the argument that post-commercialization monitoring systems are necessary in order to detect and respond to unanticipated difficulties, and to validate and improve the pre-commercialization review process. Part V presents a final regulatory scheme and a preliminary evaluation of the statutory support for such a scheme.

## I. The “Coordinated Framework” and Regulation of Pharm Plants

In the first part of this paper I review the regulatory oversight for pharm plants. With a few notable exceptions, pharm plants are regulated under the same set of statutes and rules as other transgenic plants. The basic regulatory structure was set down in the late 1980s and the early 1990s. In 1986, the Office of Science and Technology Policy (OSTP) released a “Coordinated Framework” detailing the regulatory responsibilities of FDA, EPA and USDA (particularly the Animal and Plant Health Inspection Agency, APHIS).<sup>13</sup> This framework has been reviewed extensively, and will be summarized only briefly here.<sup>14</sup>

### A. Food and Drug Administration

FDA asserts regulatory authority over foods containing transgenic plant material under the Federal Food, Drug and Cosmetic Act (“FFDCA”). FDA authority derives primarily from two sections of the FFDCA, 21 U.S.C. §342<sup>15</sup>, pertaining to adulterated food, and 21 U.S.C. § 348<sup>16</sup>, pertaining to food additives.

Section 342 empowers FDA to initiate an enforcement action against foods containing an “added” substance that is present at levels that “may be injurious to health”. The term “added” has been interpreted expansively and now includes substances that are added only indirectly.<sup>17</sup> For example, environmental contaminants,

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<sup>13</sup> *Coordinated Framework for Regulation of Biotechnology*, 51 FR 23302, OSTP, June 26, 1986.

<sup>14</sup> See Pew Initiative on Food and Biotechnology, *Issues in the Regulation of Genetically Engineered Plants and Animals*, April 2004. See also, NRC 2002, *supra* note 7, at 101-20.

<sup>15</sup> 21 U.S.C. §342, FFDCA § 402.

<sup>16</sup> 21 U.S.C. §348, FFDCA § 408.

<sup>17</sup> 39 FR 42743. See also Peter Barton Hutt and Richard A. Merrill, *Food and Drug Law: Cases and Materials*, 2<sup>nd</sup> Ed. New York, New York. Foundation Press, 1991, at 298-99.

such as mercury, are “added” under section 342 even though no person intentionally added these substances to food.<sup>18</sup> With respect to transgenic plants, FDA stated, “If a food produced by new biotechnology contains a higher level of a substance than it might ordinarily have, then the level ‘may be injurious to health’ and the agency could regulate the product under section 402(a)(1) [21 U.S.C. §342(a)(1)].”<sup>19</sup> Where a substance “may be injurious to health” and is difficult to remove through improved food production techniques, FDA may establish a tolerance level, demarcating the maximum allowable amount of the substance in food.<sup>20</sup> FDA expends considerable resources to research and establish tolerance levels, and FDA has the option instead of setting action levels. Action levels are generally conservative safety levels that, if exceeded, trigger the research effort to establish a tolerance.<sup>21</sup> Enforcement under section 342 is only against foods that have already entered the marketplace. With respect to a transgenic plant, the offending substance would have to be detected in a food product before FDA could initiate an enforcement action.

Further, FDA has authority under the food additive provision, 21 U.S.C. §348. The term food additive is defined as “any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food”, with the broad exception that any food that is generally recognized as safe (GRAS) is not a food additive.<sup>22</sup> In a “Statement of Policy” issued in 1992, FDA noted that many substances produced in transgenic plants are likely to be generally comparable to a substance that is already present in foods.<sup>23</sup> FDA presumes that such substances are GRAS. However, FDA went on to state, “It is possible, however, that the intended expression product in a food could be [one] that differs significantly... from substances found currently in food. Such substances may not be GRAS and may require regulation as a food additive.”<sup>24</sup> In September 2000, this

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<sup>18</sup>See *United States v. Anderson Seafoods, Inc.* 622 F.2d 157 (5<sup>th</sup> Cir. 1980).

<sup>19</sup>Coordinated Framework, *supra* note 13, at 23312.

<sup>20</sup>21 C.F.R. §109.6.

<sup>21</sup>Hutt, *supra* note 17, at 299.

<sup>22</sup>21 U.S.C. §321(s). FFDCA § 201(s).

<sup>23</sup>*Statement of Policy: Foods Derived From New Plant Varieties*, 57 FR 22984 at 22990, FDA, May 25, 1992.

<sup>24</sup>*Id.*

policy withstood a court challenge brought by a coalition of concerned groups and individuals.<sup>25</sup>

In contrast to the post-market regulatory power under section 342, the food additive provisions create a system of pre-market review administered by FDA. A company that petitions for food additive status has the burden of providing sufficient evidence to establish safe levels for the food additive.<sup>26</sup> The expense of establishing a tolerance under section 342 falls primarily on FDA, while the regulated party bears much of the cost of obtaining a food additive petition. Food additive petitions are significant procedures, estimated to cost roughly \$15 to \$25 million, over a span of years.<sup>27</sup>

For the most part, FDA has reviewed food safety issues for transgenic plants under a voluntary consultation process.<sup>28</sup> In commercializing the Flavr Savr tomato, the manufacturer and FDA conducted an extensive consultation to resolve safety issues. The consultation culminated in an approved food additive petition for an antibiotic resistance transgene that was present in the tomato.<sup>29</sup> A Food Advisory Committee, consisting of outside experts, recommended that FDA adopt a streamlined process for approving future transgenic plants. In response FDA established an informal and voluntary process by which firms can submit safety data.<sup>30</sup> As of 2001, FDA had completed 45 consultations and expressed the belief that all developers of transgenic foods marketed in the U.S. had consulted FDA.<sup>31</sup> In 2001, FDA proposed to replace the voluntary consultation process with a mandatory submission process that would require developers of transgenic crops to submit to FDA a notice of intent and food safety data at least 120 days prior to commercialization.<sup>32</sup>

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<sup>25</sup> *Alliance for Bio-Integrity v. Shalala*, 116 F.Supp.2d (D.D.C. 2000).

<sup>26</sup> Pew Initiative, *supra* note 14, at 73.

<sup>27</sup> *Id.*

<sup>28</sup> *Premarket Notice Concerning Bioengineered Foods*, 66 FR 4706 at 478, FDA, Jan. 18, 2001.

<sup>29</sup> *Safety Assurance of Foods Derived by Modern Biotechnology in the United States*, Center for Food Safety and Applied Nutrition, FDA, July 1996.

<sup>30</sup> *Premarket Notice*, *supra* note 28.

<sup>31</sup> *Id.* at 478.

<sup>32</sup> *Id.*

FDA has not codified this proposal into a regulation.

For pharm plants that are not intended for use in food, FDA post-market authority under section 342 remains essentially unchanged. If a pharm plant or a transgene encoding a non-food product accidentally enters the food supply, FDA would have the authority to evaluate the situation and, as appropriate, initiate an enforcement action against the allegedly adulterated food. FDA exercised this power to recall food contaminated with the StarLink transgenic corn. StarLink corn contained a pesticidal protein not approved at any concentration for human consumption.<sup>33</sup>

FDA remains committed to enforcing post-commercialization food safety standards under section 342. In 2002, FDA, EPA and USDA released guidelines for plants bioengineered to produce drugs and biologics.<sup>34</sup> The guidelines contain almost no reference to food safety except to say, “When the bioengineered pharmaceutical plant is from a species that is used for food or feed, 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. The presence of any such material in food or feed could render such products adulterated under the FD&C Act.”<sup>35</sup> Thus, FDA’s most recent statement on the subject emphasizes post-commercialization enforcement.

The food additive statutes provide a less certain grant of power to FDA over plants not intended for food. The definition of a food additive sets out two primary types of additives that will be subject to regulation.<sup>36</sup> “Intentional” additives are those that are intentionally placed in food. “Incidental” additives are those that are reasonably expected to affect food, and legislative records show that the “incidental” category was created with packaging materials and manufacturing processes in mind.<sup>37</sup> In *Natick Paperboard*,

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<sup>33</sup>See StarLink discussion, *infra*.

<sup>34</sup>Draft Guidance for Industry, *Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals*, September 2002. Accessed at [www.fda.gov/cber/gdlns/bioplant.htm](http://www.fda.gov/cber/gdlns/bioplant.htm).

<sup>35</sup>*Id.*

<sup>36</sup>*Natick Paperboard Corp. v. Weinberger*, 525 F.2d 1103, 1107 (1<sup>st</sup> Cir. 1975)

<sup>37</sup>*Id.* citing H. Rep. No. 2284, 85th Cong., 2d Sess. 3 (1958); S. Rep. No. 2422, 85th Cong., 2d Sess. 4, 5 (1958).

the court considered whether paper packaging material containing high levels of polychlorinated biphenyls would be considered a food additive and could be subject to FDA enforcement even prior to its use as a food packaging. The court determined that the paperboard was a food additive, as long as there was reasonable expectation that it would be used for food packaging.<sup>38</sup> Paperboard to be used for other purposes would not come under FDA jurisdiction.<sup>39</sup> The court seems to suggest that factors to be weighed in determining the “reasonably expected” portion of the test might include the intent of the manufacturer as well as the actual likelihood of the event.<sup>40</sup> The analogy to pharm plants is not perfect, but it is likely that if there is no reasonable expectation that a pharm plant will become part of food, then the food additive provisions would be inapplicable. The degree to which pharm plants can be segregated from food plants would surely be a significant factor in determining the applicability of the food additive provisions. If pharm plants can be perfectly contained, there would be no reasonable expectation that the plant or the transgene would come in contact with food and no reason, or power, to regulate such plants as food additives. The notion that pharm plants can be absolutely prevented from commingling with food products is consistent with present regulatory policy, and perhaps it is for this reason that FDA has never attempted to use food additive provisions to regulate pharm plants. However, there are many reasons, presented below, to believe that containment is actually far from perfect, and that there may in fact be a reasonable expectation that pharm plants would mingle with food materials. If this were the case, FDA might be able to subject non-food pharm plants to the pre-commercialization food additive review system.

Although the statutory authority for FDA’s pre-market review of pharm plants is unclear, FDA has sought to provide some pre-market safety review through voluntary proceedings. FDA has announced that it “encourages developers of bioengineered plants that are not intended for use in food or feed, but that theoretically

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<sup>38</sup>*Id.* at 1107.

<sup>39</sup>*Id.*

<sup>40</sup>*Id.* at 1108.

could enter the food or feed supply, to participate in [a] consultation program.”<sup>41</sup> However, it is notable that at least one pharm crop, corn engineered to express avidin, has been grown commercially without any apparent consultation with FDA.<sup>42</sup> At high levels avidin can cause a serious vitamin deficiency in humans.<sup>43</sup> So, it is unlikely that the voluntary system actually provides a food safety review for all pharm plants. Critics have suggested that the quality of data the FDA receives in these voluntary proceedings is inadequate to make a proper risk assessment.<sup>44</sup>

The 2002 Draft Guidelines emphasize an important additional power that FDA can exercise over pharm plants that produce pharmaceuticals: drug regulatory power under the Public Health Service Act (42 U.S.C. 262 et seq.) and the FFDCA. Under these statutes, FDA has the power to approve or not approve the sale of any drug and FDA can also exercise control over drug manufacturing processes. In fact, the bulk of the Guidelines are devoted suggestions for sound “manufacturing” processes in plants, emphasizing reproducibility, suggesting that FDA does intend to assert control over the drug “manufacturing” that takes place in plants.<sup>45</sup>

In sum, the regulatory scheme implemented by FDA includes voluntary pre-market food safety assessment for pharm plants, mandatory pre-market drug safety review for drug products derived from pharm plants, and the threat of enforcement proceedings in the event that non-food plant material or transgenes enter the food supply.

Intriguingly, FDA authority to require pre-market regulation of pharm plants as food additives may depend on the degree of containment that is reasonably expected. However, as a practical matter, FDA probably

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<sup>41</sup>Premarket Notice, *supra* note 28, at 4714.

<sup>42</sup>NRC 2002, *supra* note 7, at 108-9.

<sup>43</sup>*Id.*

<sup>44</sup>Jaffe, *supra* note 12.

<sup>45</sup>Draft Guidelines, *supra* note 33.

has sufficient power to force pharm plant developers into pre-market review system anyway.

## **B. United States Department of Agriculture**

USDA has regulatory authority over field releases of transgenic “plant pests” under the Federal Plant Pest Act and the Plant Quarantine Act<sup>46</sup> (later superceded by the Plant Protection Act<sup>47</sup>). The act is administered by the Animal and Plant Health Inspection Service (“APHIS”) within USDA. APHIS formulated final regulations under this statutory authority, presented in 7 CFR part 340.<sup>48</sup> APHIS asserted authority only over “regulated articles”, which are essentially organisms that are, or contain, “plant pests”.<sup>49</sup> In reviewing these regulations, the National Research Council wrote, “The definition of plant pest is in many ways extremely broad but in other ways surprisingly restricted. . . [I]f a transgenic plant was created from a nonweedy species without the insertion of genes from a plant pest and it was transformed without the intervention of a plant pest, it would not necessarily be considered a regulated article.” NRC expresses the concern that the presence of a “plant pest” in many transgenic plants is merely a matter of happenstance resulting from the choice of technology during the engineering of the plant. The “plant pest” portions are used merely as tools and, in many instances, could be replaced by non-plant pest tools, possibly eliminating USDA’s regulatory hold over the plant. However, NRC notes that, “In such cases, the creators of transgenic

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<sup>46</sup>Coordinated Framework, *supra* note 13, at 23342.

<sup>47</sup> U.S.C. 7701 et seq. 7 U.S.C. § 7758 specifically repeals the previous statutes, although § 7758(c) preserves regulations promulgated under the earlier laws until such time as new regulations were approved. No new regulations have been generated and so the older laws are essentially still in effect.

<sup>48</sup>7 C.F.R. § 340.

<sup>49</sup>“Regulated article” is defined as: “Any organism which has been altered or produced through genetic engineering, if the donor organism, recipient organism, or vector or vector agent belongs to any genus or taxon designated in a list of taxa known to have plant pests and meets the definition of a plant pest. . . .”

Plant pests are defined to include essentially any organism, including viruses, known to directly or indirectly damage plants or products of plants. Most methods for generating a transgenic plant involve the use of a DNA fragment from a virus or bacterium that is a plant pest. Even though this DNA fragment may be largely incidental to the trait being engineered, it provides a regulatory hook that APHIS relies upon to assert jurisdiction.

plants to be field released apparently have always sent a ‘courtesy’ notification or permit application to APHIS.”<sup>50</sup> Thus, despite a possible loophole in the definitions, it does not appear that industry participants are attempting to escape regulation in this manner.

APHIS jurisdiction attaches when a party wishes to grow a transgenic plant in the field as part of interstate commerce. APHIS can impose one of three levels of regulation: notification, permit or deregulation. Notification is the most permissive regulatory scheme.<sup>51</sup> The party need only notify APHIS of the planned field release and provide data sufficient to satisfy a set of six criteria.<sup>52</sup> Plants containing a transgene that encodes a product intended for pharmaceutical use are specifically excluded from the notice system and can only be grown in the open field under a more stringent regulatory procedure.<sup>53</sup> An interim rule released August 6, 2003, also excluded plants engineered to produce industrial compounds from the notice system.<sup>54</sup> Industrial compounds are defined as those that meet all three of the following criteria: (1) the compound is new to the plant; (2) the new compound has not been used commonly in food or feed; and (3) the new compound is being expressed for a non-food or non-feed industrial use.<sup>55</sup>

A pharm plant may only be grown in the field under a permit procedure, described in 7 CFR 340.4.<sup>56</sup> Under this procedure, a party submits information describing the transgenic plant, the nature of the field growth, the intended use for the plant and containment measures to be used.<sup>57</sup> According to the National Research Council, which has reviewed APHIS procedures, the primary concern in the permit process is to ensure the

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<sup>50</sup>NRC 2002, *supra* note 7, at 107.

<sup>51</sup>7 C.F.R. 340.3.

<sup>52</sup>*Id.*

<sup>53</sup>7 C.F.R. 340.3(b)(4)(iii).

<sup>54</sup>*Introductions of Plants Genetically Engineered to Produce Industrial Compounds*, 68 FR 46434, APHIS, August 6, 2003.

<sup>55</sup>*Id.* at 46435.

<sup>56</sup>7 CFR 340.4

<sup>57</sup>*Id.*

appropriate containment of the plant to minimize the chance of any effects outside the test site.<sup>58</sup> A permit may be issued with various constraints and requirements, particularly with respect to the duration, location and containment of the transgenic plant.<sup>59</sup> APHIS has the right to inspect for permit compliance.<sup>60</sup>

In 2003, responding to a variety of concerns, APHIS announced new permit conditions for field testing of all plants engineered to produce pharmaceutical and/or industrial compounds.<sup>61</sup> These conditions include:

1.

A perimeter fallow zone of 50 feet;

2.

A possible requirement to allow the test field to lie fallow in cases where a pharm plant could grow up in the season following the test (a “volunteer” plant);

3. Dedicated planter and harvester machinery for use with the engineered plants only; and

4.

Dedicated facilities for storage of equipment and plant material during the field test is required, along with specific cleaning and drying techniques for the harvested crops.<sup>62</sup>

With respect to corn specifically, APHIS suggests two control mechanisms, (1) a distance of at least one mile between pharm corn and any other corn, or (2) manual bagging over corn tassels to reduce pollen drift, with

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<sup>58</sup>NRC 2002, *supra* note 7, at 109.

<sup>59</sup>*Id.*

<sup>60</sup>7 CFR 340.4(d).

<sup>61</sup>*Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds*, 68 FR 11337 at 11338, APHIS, March 10, 2003.

a 28 day offset from the planting schedule of any corn growing at a distance of one-half mile to a mile.<sup>63</sup> The 28 day offset for the planting schedule is intended to ensure that, when the pharm corn is releasing pollen, traditional corn in the area is not at a stage where it is receptive to pollen. In addition, APHIS announced its intention to increase the number of site inspections to enforce compliance with the permit conditions.<sup>64</sup> The third tier of the APHIS system is the petition for determination of nonregulated status, under 7 C.F.R. 340.6.<sup>65</sup> A transgenic plant that has achieved nonregulated status can be grown without any further USDA oversight. All of the widely grown soybean, corn, cotton and canola varieties have been granted non-regulated status.<sup>66</sup> APHIS has indicated that nonregulated status is not available to pharm plants.

### **C. Environmental Protection Agency**

EPA authority over transgenic plants is not expected to extend significantly to pharm plants. However, EPA oversight played a prominent role in the StarLink incident, discussed below, and so a brief overview is provided. EPA regulates transgenic plants that are engineered to produce a pesticidal product under the Federal Insecticide, Fungicide and Rodenticide Act (“FIFRA”).<sup>67</sup> These pesticidal products are often referred to as Plant Incorporated Protectants, or “PIPs”. EPA is responsible for establishing the safety of PIPs both with respect to human health<sup>68</sup> and the environment<sup>69</sup>. EPA oversight under FIFRA dovetails with FDA enforcement of adulterated foods. If a pesticide in a food exceeds the tolerance set by EPA, the food is adulterated for the purpose of FDA and enforcement action may be taken.<sup>70</sup> Many plants are

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<sup>63</sup>*Id.* at 11388.

<sup>64</sup>*Id.* at 11388-89.

<sup>65</sup>7 C.F.R. 340.6.

<sup>66</sup>NRC 2002, *supra* note 7, at 111.

<sup>67</sup>7 U.S.C. § 135 et seq.

<sup>68</sup>21 U.S.C. § 346a.

<sup>69</sup>7 U.S.C. § 136a.

<sup>70</sup>21 U.S.C. §§ 342 and 346a.

engineered to express pesticidal proteins. For example, the bacterium *Bacillus thuringensis* produces several toxins (“Bt toxins”) that are lethal to moths and butterflies, many of which are pests.<sup>71</sup> Plants have been engineered to express Bt toxins to assist with pest control.<sup>72</sup> The pesticidal transgene is regulated by EPA and evaluated for safety in the environment and the food supply.

EPA also has authority over chemical substances under the Toxic Substances Control Act (“TSCA”).<sup>73</sup> <sup>74</sup> Drugs and food are excluded from the substances that are regulated under TSCA.<sup>75</sup> Plants engineered to produce industrial products presumably could be regulated under TSCA.<sup>76</sup>

#### **D. Summary of Regulations for Pharm Plants**

In summary, APHIS and FDA have the primary regulatory authority relating to pharm plants.

APHIS administers the permits that are required for open field growth of pharm plants. In setting conditions for permits, APHIS is primarily interested in containment measures that are intended to prevent mixing between pharm crops and food crops.

FDA operates a voluntary system by which a developer of a pharm plant for a non-food purpose may seek

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<sup>71</sup>National Research Council, Genetically Modified Pest-Protected Plants: Science and Regulation, National Academy Press (Washington D.C. 2000), at 27.

<sup>72</sup>*Id.*

<sup>73</sup>15 U.S.C. § 2601 et seq.

<sup>74</sup>Coordinated Framework, *supra* note 13, at 23315. See also Pew Initiative, *supra* note 14.

<sup>75</sup>15 U.S.C. § 2602(2)(A).

<sup>76</sup>Pew Initiative, *supra* note 14, at 48.

FDA input on food safety issues. FDA also expresses willingness to take post-commercialization enforcement action against food that is adulterated by non-food pharm plants. Furthermore, FDA will review all drugs obtained from pharm plants for safety and efficacy.

Under this regulatory system, the only guaranteed pre-market oversight of pharm plants is on the issue of containment. No risk assessment of health or environmental risks will be made consistently. Two critical questions arise from this evaluation of the present regulatory scheme for pharm plants. First, do the containment measures work? And second, if containment measures do not work, is post-market enforcement action likely to control any risks to the food supply? An analysis of actual field experience with transgenic plants suggests that the answer to both of these questions is no.

## **II. Containment and Unpredictability: Lessons from the Field**

The effectiveness of containment measures in preventing the escape of transgenic plants has been difficult to address through theoretical models and small experimental field sites.<sup>77</sup> As will be seen from the materials below, the variability of field conditions often defy prediction. Fortunately, at present the first generation of transgenic plants have been widely cultivated for nearly a decade, and there has been some field containment experience with pharm plants as well. Additionally, scientists have generated considerable data on the field behavior of transgenic plants and their conventional brethren. A review of these studies provides considerable insight into the effectiveness of containment measures used for transgenic plants.

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<sup>77</sup>Mary Rieger, Michael Lamond, et al. *Pollen-mediated movement of herbicide resistance between commercial canola fields*. SCIENCE June 28, 2002 at 2386.

## A. ProdiGene, Inc.: Wandering Off the Pharm

The most direct indication that the containment measures used with pharm plants may not be effective comes from the near escape of corn plants that were engineered for expression of a protein for a swine vaccine.

The corn was engineered by ProdiGene, Inc., an agricultural biotechnology company that has pioneered the business of pharming.<sup>78</sup> Prodigene received approval for several small open field plots of corn engineered to express pharmaceutical or veterinary products. On November 13, 2002, USDA announced that it had discovered permit violations at two pharm corn sites under cultivation by ProdiGene. The plants were designed to provide an oral vaccine to swine for the prevention of Transmissible Gastroenteritis Virus (TGEV).<sup>79</sup> At a site in Nebraska, pharm corn had been planted in 2001, and non-pharm soybean had been planted in the following year.<sup>80</sup> An inspection revealed that corn was growing in the soybean field, presumably from seed set down in the previous growing season. This situation, where corn grows up from seed from the previous season, is familiar and the plants are referred to as “volunteer” corn. The presence of volunteer corn, presumably pharm corn, was a violation of the APHIS permit. ProdiGene was instructed to destroy the soybeans. However, the soybeans were harvested and moved to a storage facility where they were mixed with 500,000 bushels of soybeans.<sup>81</sup> Under a consent agreement, ProdiGene agreed to reimburse USDA for the cost of destroying the soybeans.<sup>82</sup> The destroyed soybeans were valued at approximately \$3.5 million.<sup>83</sup>

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<sup>78</sup>www.prodigene.com.

<sup>79</sup>.See U.S. Patent Nos. 6,034,298 and 5,914,123 See also Greg Burns and Julie Deardorff, *Modified Crops Raise Fears of Contamination*, CHICAGO TRIBUNE, November 18, 2002.

<sup>80</sup>USDA INVESTIGATES BIOTECH COMPANY FOR POSSIBLE PERMIT VIOLATIONS, APHIS NEWS, Nov. 13, 2002. Accessed at [www.biotech.wisc.edu/Education/prodigene.html](http://www.biotech.wisc.edu/Education/prodigene.html).

<sup>81</sup>*Id.*

<sup>82</sup>USDA Announces Actions Regarding Plant Protection Act Violations Involving ProdiGene, Inc., USDA PRESS RELEASE No. 4098.02, December 6, 2002. Accessed at [www.usda.gov/news/releases/2002/12/0498.htm](http://www.usda.gov/news/releases/2002/12/0498.htm).

<sup>83</sup>Norman Ellstrand, *Going to “Great Lengths” to Prevent the Escape of Genes that Produce Specialty Chemicals*, PLANT PHYSIOLOGY, August 2003 at 1770.

Inspectors also discovered volunteer corn at another ProdiGene pharm corn site in Iowa. This also was a violation of permit conditions, and 155 acres of surrounding corn were destroyed.<sup>84</sup> ProdiGene also agreed to pay a civil fine of \$250,000 in settlement of the two incidents.<sup>85</sup>

The ProdiGene incidents illustrate weaknesses in the containment systems employed by APHIS. First, the mechanisms that were relied upon in the ProdiGene incident required compliance on the part of the regulated parties.<sup>86</sup> ProdiGene committed at least three permit violations in these incidents, allowing the growth of tassled (i.e., pollen bearing) pharm corn in a season after the permits had expired.<sup>87</sup>

The ProdiGene incidents took place under fairly tight permit regulations designed for pharm corn, and thus are most directly predictive of the success of future pharm plant containment measures. It is notable that the pharm plant permit conditions recently proposed by APHIS rely almost entirely on containment measures that require compliance by regulated parties.<sup>88</sup> The failure of the regulated parties to conform to the stringent permit conditions casts serious doubt on the effectiveness of any containment measure that relies upon human behavior.

## **B. StarLink Corn: The Early Warning Signs**

First generation transgenic plants have been subject to relatively relaxed containment requirements, relative to pharm plants. Nonetheless, the extensive experience with first generation transgenic plants provides insight into foreseeable difficulties in preventing the spread of pharm transgenes.

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<sup>84</sup>APHIS NEWS, *supra* note 80.

<sup>85</sup>USDA PRESS RELEASE, *supra* note 82.

<sup>86</sup>*Id.*

<sup>87</sup>*Id.*

<sup>88</sup>Field Testing, *supra* note 61, at 11338.

In 1998, AgrEvo USA Co. obtained the final regulatory approvals for commercialization of the now infamous StarLink corn.<sup>89</sup> StarLink corn is engineered to express a toxin of *Bacillus thuringiensis* (a “Bt” toxin), called Cry9C. This toxin selectively kills Lepidopteran insects (primarily moths and butterflies).<sup>90</sup> Bt corn varieties were designed to provide resistance to the caterpillar phase of the European corn borer moth.<sup>91</sup> Bt toxins are biodegradable and highly selective, and farmers have used *B. thuringiensis* bacteria for decades as a biological pesticidal agent applied directly to crops.<sup>92</sup> Partly because Bt toxin residues from these biological pesticide applications were already known to be safe in foods, EPA had permitted commercialization of other transgenic crops engineered to express Bt toxins.<sup>93</sup>

Cry9C is different from previously approved Bt toxins, and EPA refused to register StarLink for use in human food products.<sup>94</sup> EPA was concerned that Cry9C exhibited properties that are correlated with properties of allergenic proteins, and a Scientific Advisory Panel could not conclude that Cry9C was not a food allergen.<sup>95</sup> AgrEvo requested registration only for use in animal feed. In 1998, EPA approved the so-called “split registration”, allowing the commercialization of StarLink corn exclusively for use in animal feed.<sup>96</sup> Pursuant to the animal feed restriction, APHIS awarded StarLink deregulated status.<sup>97</sup>

EPA discussed various routes by which humans might be exposed to Cry9C, including exposure to skin, inhalation and exposure in drinking water.<sup>98</sup> This discussion is notable in view of later events. Each of the

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<sup>89</sup>For a detailed account of the StarLink incident, see Rebecca M. Bratspies, *Myths of Voluntary Compliance: Lessons from the StarLink Corn Fiasco*, 27 Wm. & Mary Envtl. L. & Pol’y Rev. 593, Spring 2003.

<sup>90</sup>National Research Council, Genetically Modified Pest-Protected Plants: Science and Regulation, National Academy Press (Washington, D.C., 2000).

<sup>91</sup>*Id.*

<sup>92</sup>*Plant Pesticide Bacillus thuringiensis CryIA(b) Delta-Endotoxin and the Genetic Material Necessary for its Production (Plasmid Vector pCIB4431) in Corn*, 60 FR 42443 at 42444, EPA, Aug. 16, 1995.

<sup>93</sup>*Id.*

<sup>94</sup>Bratspies, *supra* note 89, at 594.

<sup>95</sup>*Food Allergenicity of Cry9C Endotoxin and Other Non-digestible Proteins*, SAP Report No. 2000-01A, June 29, 2000.

<sup>96</sup>*Plant Pesticide Bacillus thuringiensis CryIA(b) Delta-Endotoxin and the Genetic Material Necessary for its Production in Corn; Exemption from the Requirement for a Tolerance*, 63 FR 28258, EPA, May 22, 1998.

<sup>97</sup>63 FR 27041.

<sup>98</sup>Bt Exemption, *supra* note 96, at 28259.

exposure were deemed unlikely. On the subject of oral exposure, EPA reported, “Minimal to non-existent oral exposure could occur from ingestion of meat, poultry, eggs or milk from animals fed corn containing the plant-pesticide. . . This is viewed as a remote possibility due to. . . the anticipated degradation and elimination of the Cry9C protein by the animal.”<sup>99</sup> Thus the only oral exposure route considered was the indirect exposure resulting from consuming food from animals that were fed StarLink corn. Among all of the exposure risks contemplated by the EPA, direct entry of StarLink corn into the human food supply was not even mentioned as a possibility.

In September, 2000, after StarLink had been grown commercially for three seasons, a non-profit organization, Genetically Engineered Food Alert, reported to the Washington Post that Cry9C DNA had been detected in taco shells.<sup>100</sup> These results were verified by FDA and USDA. The Grain Inspection Service conducted roughly 110,000 grain tests for the presence of Cry9C across the U.S. in late 2000 and early 2001.<sup>101</sup> Of these tests, about one-tenth were positive, indicating a rapid and extensive spread of the transgene through the agricultural system.<sup>102</sup>

Because the Cry9C protein had not received a tolerance or exemption for human food, the contaminated food was automatically adulterated and illegal, triggering a recall by food manufacturers in the United States and abroad.<sup>103</sup> Millions of dollars worth of finished food product were destroyed.<sup>104</sup> Aventis CropScience (AgrEvo’s corporate successor to StarLink) and USDA initiated a buyback program to purchase contaminated corn and redirect the corn to the animal feed market.<sup>105</sup> Decreases in the export of U.S. corn to Japan, South Korea and Europe are all attributed to the StarLink incident.<sup>106</sup> A lawsuit by consumers

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<sup>99</sup>*Id.*

<sup>100</sup>Marc Kaufman, *Biotech Critics Cite Unapproved Corn in Taco Shells*, WASHINGTON POST, September 18, 2000.

<sup>101</sup>Alexander Haslberger, *Letter to the Editor*, NATURE BIOTECHNOLOGY, July 2001. *See also* Anthony Shadid, *Genetically Engineered Corn Appears in One-Tenth of Grain Tests*, BOSTON GLOBE, May 3, 2001.

<sup>102</sup>*Id.*

<sup>103</sup>Pew Initiative, *supra* note 14, at 85.

<sup>104</sup>K.T. Arasu, *Aventis says has paid millions over gene-altered corn*, REUTERS, January 5, 2001.

<sup>105</sup>Scott Killman, *Aventis Is Suspending Seed Sales Of Genetically Engineered Corn*, WALL STREET JOURNAL, September 27, 2000.

<sup>106</sup>William Lin, Gregory K. Price, and Edward Allen, *Impacts on the U.S. Corn Market and World Trade*, USDA’s Feed

against manufacturers of the contaminated food settled for \$9 million, and lawsuits by farmers against Aventis CropScience have settled for a reported \$110 million.<sup>107</sup> <sup>108</sup>

The StarLink incident stands as a lasting example of failed control systems and illustrates the difficulty that a regulatory agency faces in predicting the risks associated with a transgenic crop. Aventis CropScience has been pinned with much responsibility for the incident. As alleged by plaintiff farmers in a class action lawsuit, Aventis CropScience failed to notify farmers of the restrictions set in place by EPA to prevent commingling with the food supply.<sup>109</sup> These restrictions included requirements for a 660 foot buffer zone between StarLink and non-StarLink crops and appropriate post-harvest handling and marketing procedures.<sup>110</sup> Allegedly, Aventis CropScience actively informed farmers that StarLink was fit for human consumption and need not be segregated from other crops.<sup>111</sup>

It is startling how wildly EPA misjudged the likelihood that StarLink corn would enter the human food supply. By denying a tolerance for StarLink corn in human food, EPA created a black-and-white legal situation. Food contaminated with even trace amounts of Cry9C would immediately become legally adulterated and subject to recall or destruction. In the end, there are no verified adverse health consequences attributed to Cry9C<sup>112</sup>, and all of the economic damaged suffered could be attributed to a mixture of under-regulation (lack of containment) and over-regulation (no tolerance level set for Cry9C in food). If one assumes that EPA felt confident that the guidelines promulgated for containment of StarLink were sufficient to prevent the escape into food products and to avoid the type of economic disaster that in fact occurred, then EPA's predictions of risk were quite inaccurate.

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Yearbook, 2001, pp. 40-48.

<sup>107</sup>Mike Robinson, *Judge approves \$9 million settlement in bioengineered-corn suit*, Associated Press, March 8, 2002.

<sup>108</sup>K.T. Arasu, *US farmers reach \$110 million StarLink settlement*, REUTERS, Feb 10, 2003.

<sup>109</sup>*In re StarLink Corn Products Liability Litigation*, 212 F.Supp.2d. 828, at 834-35 (D. N.Ill. 2002).

<sup>110</sup>*Id.*

<sup>111</sup>*Id.*

<sup>112</sup>*Investigation of Human Health Effects Associated with Potential Exposure to Genetically Modified Corn*, A Report to the U.S. Food and Drug Administration from the Centers for Disease Control and Prevention, June 2001.

Compliance failures by Aventis CropScience may have been a major contributing factor to the contamination of the food supply. However, a review of scientific research on the commingling of transgenic and conventional crops, presented below, reveals that, in corn and many other plant species, transgenes move from plant to plant frequently, seemingly without regard for human efforts at confinement. In hindsight, EPA's reliance on a 660-foot buffer zone to protect the food supply was painfully naïve.

### C. The Seed Supply

The path of a grain crop from seed to cereal bowl was, even in the pre-StarLink days, subject to considerable control efforts. Evidence now shows that the commingling of transgenic and conventional crops has occurred at nearly every step of the process. The path begins with the growth of seed crop, meaning crop that will be sold as seed to farmers. In April 2004 the Union of Concerned Scientists (“UCS”), a non-profit group that has advocated for tighter regulation of transgenic plants, released a pilot study indicating that there is widespread commingling of transgenic construct with organic, non-transgenic seed lots.<sup>113</sup>

Plant breeders take significant efforts to preserve the purity of seed stocks. Therefore, the UCS finding sends a particularly strong message about the ease with which transgenes evade the standard containment and segregation efforts. The Association of Official Seed Certification Agencies maintains a set of standards for seed growers.<sup>114</sup> These standards involve detailed instructions on the practices that are necessary to maintain sufficient purity in seed stocks, including prescribed growing practices, isolation from other varieties, tolerance levels for off-variety plants, etc.<sup>115</sup> Seed purity is maintained in part through a system of several different types of stock of decreasing purity.<sup>116</sup> “Breeder” seeds are the highest purity, directly controlled by the

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<sup>113</sup>Margaret Mellon and Jane Rissler, *Gone to Seed: Transgenic Contaminants in the Traditional Seed Supply*, Union of Concerned Scientists, 2004.

<sup>114</sup>*Operational Procedures, Crop Standards and Service Programs Publications*, Association of Official Seed Certifying Agencies, 2003. Accessed at [www.aosca.org](http://www.aosca.org).

<sup>115</sup>*Id.* at 149-57.

<sup>116</sup>*Id.* at 140.

institution that originally created the variety, or by a designate selected by the originating institution.<sup>117</sup> “Foundation” seed are progeny of the breeder seed that are produced under the same conditions as the breeder seed. From each batch of foundation seed, plants that are identified as particularly desirable exemplars for maintenance of the variety are used to replenish the breeder seed.<sup>118</sup> The next tier of seed is “Registered” seed, which is progeny of the Breeder or Foundation seed, but grown only in accordance with accepted procedures, not necessarily under control of the originating institution.<sup>119</sup> “Certified” seed is progeny of Breeder, Foundation or Registered seed that meets the quality standards of the certifying agency.<sup>120</sup> The bulk of commercial seed sold to farmers in a growing season is the progeny of registered seed. Farmers may also hold back a portion of the previous year’s harvest to use for seed.<sup>121</sup> For each category of seed, a tolerance for off-variety seed is set. For example, in canola (rapeseed), foundation seed is permitted to have no more than 0.05% off-types, and the tolerance for certified seed is set at 0.25%.<sup>122</sup>

UCS found that only one of six corn and soybean seed lots tested was free of DNA derived from a transgenic source.<sup>123</sup> Six of six canola seed lots contained DNA derived from a transgenic source.<sup>124</sup> Transgenic DNA was reported at levels of 0.1% to 1% in the tested seed lots.<sup>125</sup> The presence of commingling in soybeans was particularly surprising, as soybeans are predominantly self-pollinating, meaning that soybean commingling is more likely to occur as a result of mixing during human handling, as opposed to cross-hybridization mediated by pollen drifting from neighboring transgenic crop plantations.<sup>126</sup>

The UCS report is not the first documentation of transgenes commingling with conventional seed lots. In

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<sup>117</sup> *Id.*

<sup>118</sup> *Id.*

<sup>119</sup> *Id.*

<sup>120</sup> *Id.* at 141.

<sup>121</sup> A helpful summary of the seed system is provided in Mellon, *supra* note 113. Note that in the case of hybrid plants, field grown seed does not usually breed true, and farmers will rarely use this seed.

<sup>122</sup> AOSCA, *supra* note 114, at 153.

<sup>123</sup> Mellon, *supra* note 113, at 25.

<sup>124</sup> *Id.*

<sup>125</sup> *Id.*

<sup>126</sup> *Id.* at 28.

2001, USDA reported that 300,000 to 400,000 bags of seed corn had tested positive for the StarLink Cry9C gene.<sup>127</sup> USDA budgeted \$15-20 million to buy back as much of the adulterated seed corn as possible.<sup>128</sup> Certified, pedigreed conventional canola seed lots in western Canada were independently confirmed to contain genetically engineered herbicide resistance traits.<sup>129</sup>

Based on these reports, we can conclude that canola, corn and soybean farmers will begin each growing season with seeds that contain approximately a 0.1-1% unexpected transgenic content. Furthermore, we can conclude that while containment measures set by AOSCA may be sufficient to maintain separate plant varieties, these containment measures are not sufficient to eliminate crop-to-crop gene flow. Yet this is only the beginning of the agricultural cycle. During the next phase of crop growth, open field cultivation by farmers, the opportunities for mixing of transgenic varieties with each other and with conventional varieties abound.

#### **D. In the Open Field: Pollen Drift and Volunteers**

The scientific community has taken considerable efforts to evaluate pollen drift as a mechanism for transgene movement. Pollen is the male gamete produced by most plants.<sup>130</sup> Pollen may travel to another plant and fertilize the female gamete to produce a “cross-pollinated” offspring containing genetic material from both parents.<sup>131</sup> Pollen may also fertilize female gametes of the same plant, producing “self-pollinated” offspring containing the genetic material of the single parent.<sup>132</sup> Some plants predominantly self-pollinate, to the near

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<sup>127</sup>Marc Kaufmann, *Going Backwards: U.S. Will Buy Back Corn Seed: Firms to Be Compensated for Batches Mixed With Biotech Variety*, WASHINGTON POST, March 8, 2001

<sup>128</sup>*Id.*

<sup>129</sup>Van Acker, R.C., Brule-Babel, A.L., Friesen, L.F. *An Environmental Safety Assessment of Roundup Ready® Wheat: Risks for Direct Seeding Systems in Western Canada, Report prepared for The Canadian Wheat Board, For submission to: Plant Biosafety Office of the Canadian Food Inspection Agency, June 2003.*

<sup>130</sup>NRC 2002, *supra* note 7, at 67.

<sup>131</sup>*Id.*

<sup>132</sup>*Id.* at 68.

exclusion of cross-pollination, while other plants are frequent cross-pollinators.<sup>133</sup> Pollen may be spread by a number of mechanisms, including wind and pollinating insects.<sup>134</sup> Cross-pollination is thought to be a very significant issue in canola and corn. AOSCA recommends a separation of 660 feet between seed corn plots and neighboring plots.<sup>135</sup> The recommended separation for canola ranges from 660 to 1320 feet.<sup>136</sup> In Australia, scientists conducted an analysis of pollen drift from transgenic to conventional canola in the year 2000, the first year of commercial cultivation of transgenic canola on that continent.<sup>137</sup> The study encompassed a geographical area equal to roughly one-third of the continent, and involved measurements of over 48 million plants in actual commercial canola plantings.<sup>138</sup> The results showed that cross-pollination of conventional canola by transgenic canola occurred rarely, generally at rates of 0.1 – 0.2% or less, but contamination occurred over distances of 3 kilometers, far greater than the AOSCA recommendations for preserving canola seed purity.<sup>139</sup>

The experience of Canadian farmers with canola crops confirms the ease with which transgenic canola can mingle with conventional crops and even other transgenic canola varieties. In 1995, the Canadian Food Inspection Agency approved the unconfined commercial cultivation of Roundup Ready canola.<sup>140</sup> In part, CFIA anticipated that gene flow among canola crops would be contained by various provisions, including boundary regions between conventional and transgenic crops.<sup>141</sup> In the event, Roundup Ready canola spread rapidly throughout the canola crops in western Canada. Several investigators have reported that even

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<sup>133</sup> *Id.*

<sup>134</sup> Katie Eastham and Jeremy Sweet, *Genetically modified organisms (GMOs): The significance of gene flow through pollen transfer*, Environmental Issue Report 28, European Environmental Agency, Copenhagen, Denmark 2002.

<sup>135</sup> AOSCA, *supra* note, at 151.

<sup>136</sup> *Id.* at 153.

<sup>137</sup> Rieger, *supra* note 77.

<sup>138</sup> *Id.*

<sup>139</sup> *Id.* at 2387.

<sup>140</sup> *Decision Document DD95-02: Determination of Environmental Safety of Monsanto Canada Inc.'s Roundup Herbicide-Tolerant Brassica napus Canola Line GT73*, Canadian Food Inspection Agency, 1995. Available at [www.inspection.gc.ca/english/plaveg/pbo/dd](http://www.inspection.gc.ca/english/plaveg/pbo/dd).

<sup>141</sup> *Id.*

pedigreed conventional seed lots are contaminated with transgenic canola.<sup>142</sup> The adventitious transgenic canola is expected to cause contamination of most conventional canola crops at a rate of less than 1%. At this rate, and given that canola is primarily used to generate oil, which would retain no trace of the original plant genetic material, there is no realistic health concern.<sup>143</sup> However, this presents yet another instance where a regulatory agency underestimated the ability of transgenic crop to escape containment measures.

Crop-to-crop gene flow in canola has also reportedly given rise to canola plants in Canada having resistance to three different herbicides, Roundup, Liberty and Pursuit.<sup>144</sup> Two of these resistance traits are transgenes, while one is the result of more traditional approaches to crop breeding.<sup>145</sup>

Corn is also well-known to cross-pollinate. Eastham and Sweet have reviewed dozens of experiments designed to measure the distance over which corn can hybridize.<sup>146</sup> The results show that in varying studies, measurable pollination occurred at distances ranging from around 20 meters to 800 meters, and the authors conclude that small quantities of pollen are likely to travel much farther.<sup>147</sup>

Apart from the risk of crop-to-crop commingling, pollen drift represents a significant concern for the movement of transgenes into wild populations. Unlike most crops, canola has closely related wild plant varieties. Thus, transgenic canola presents risks for transgene movement both within the food supply and movement between the food supply and the environment.

Scientists in Great Britain have conducted extensive studies on pollen drift between wild and cultivated canola

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<sup>142</sup>Van Acker, *supra* note 127, at 6-7.

<sup>143</sup>*Id.*

<sup>144</sup>Mary MacArthur, *Triple-resistant canola weeds found in Alta*, WESTERN PRODUCER, Saskatchewan, Canada, February 10, 2000.

<sup>145</sup>Norman Ellstrand, *When Transgenes Wander, Should We Worry?*, PLANT PHYSIOLOGY, April 2001, 1543-45.

<sup>146</sup>Eastham, *supra* note 134, at 38.

<sup>147</sup>*Id.* at 41.

varieties. In Great Britain, the agricultural canola plant, *Brassica rapa* is known to cross-pollinate with the wild species *Brassica napus*. Researches measured actual cross-pollination rates between agricultural and wild species at several areas where the two plants grow in close proximity and over a period of several years. Then, using large scale satellite images, the researches extrapolated to calculate an estimated nationwide rate of cross-hybridization into the wild species. The result suggested an annual cross-hybridization rate of about 40,000 per year.<sup>148</sup>

Sunflowers represent another example of a crop that undergoes extensive pollen-mediated gene flow. There are several wild varieties of sunflower that grow in the same areas as the cultivated plant. Studies in Canada and North Dakota show that cross-hybridization is extensive.<sup>149</sup> The authors concluded, “[T]ransgenes in cultivated sunflowers should readily introgress into sympatric wild populations.”<sup>150</sup>

Several plants have been identified as relatively low risks for pollen-mediated transgene spread. These include potato, soybean and rice. However, the lack of predictability associated with even these plants is surprising. As noted above, the Union of Concerned Scientists observed transgene contamination in soybean seed lots. In the case of potatoes, many field studies have shown a maximum pollen drift distance of twenty meters, but a single study showed 31% cross-pollination at a distance of 1000 meters!<sup>151</sup> The remarkably different result was attributed to high levels of a pollen carrying insect, the pollen beetle.<sup>152</sup> This illustrates the difficulty of accounting for all factors in a field grown crop; a normal natural occurrence, such as pollen beetles, may cause considerable variation from conditions that were used in controlled tests.

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<sup>148</sup>Wilkinson, M. J., Elliott, L.J., et al. *Hybridization Between Brassica napus and B. rapa on a National Scale in the United Kingdom*, SCIENCE, October 17, 2003, at 457.

<sup>149</sup>Linder, C.R., Taha, I., Seiler, G.J., Snow, A.A., Riesenber, L. H, *Long-term introgression of crop genes into wild sunflower populations*, THEOR. APPL. GENET., 1998, at 339.

<sup>150</sup>*Id.* at 339.

<sup>151</sup>Eastham, *supra* note 134, at 37.

<sup>152</sup>*Id.*

In addition to pollen drift, contamination of open field crops can occur because of volunteer plants. Anytime a field is planted in successive seasons, there is a risk that seed from a previous season will grow in the next season. These plants are referred to as “volunteers”. If precisely the same variety of crop is planted in successive years, the volunteer plants will not introduce any significant impurity. However, crops are often rotated, and when new varieties are planted, volunteers of a previous variety are likely to be mixed in with the new variety. The risk of volunteer contamination is recognized by the AOSCA guidelines, which specify a period of continuous years that a site should be used to establish a pure seed variety, thus diluting volunteers over time.<sup>153</sup> Likewise, the ProdiGene incidents illustrate the potential for volunteer pharm crops to contaminate the food supply, or worse, cross-hybridize with neighboring plants.

#### **E. The Human Factor**

During cultivation and harvesting, transgenic plants come into contact with another important catalyst for gene flow: human beings. A review of notable transgene escapes reveals that people in positions of responsibility for the stewardship of transgenic plants repeatedly fail to discharge their duties. APHIS reports a non-compliance rate in the range of 2% for plants regulated under the field test permit program.<sup>154</sup> However, as the StarLink incident highlights, enforcement and detection of violations is far from perfect. In the StarLink incident, Aventis CropScience was charged with providing farmers with information regarding the proper management and use of StarLink corn.<sup>155</sup> Instead, the seed provider appears to have provided almost no information to farmers, and may not even have informed them of the restriction to animal feed only.<sup>156</sup> Similarly, the ProdiGene incidents were marked by non-compliance.

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<sup>153</sup>AOSCA, *supra* note 114, at 150.

<sup>154</sup>Biotechnology Regulatory Services, *Compliance and Enforcement*, USDA, APHIS. Accessed at <http://www.aphis.usda.gov/brs/compliance.html>.

<sup>155</sup>Bratspies, *supra* note 89, at 630.

<sup>156</sup>*Id.*

The matter of human behavior becomes more troubling on the international stage. To the extent that other countries begin to grow pharm crops, it is unclear whether adequate regulatory measures will be set in place, or enforced. Brazil does not permit the cultivation of transgenic crops except under a program of temporary experimental permits termed “RETs”.<sup>157</sup> However, many farmers are operating without RETs, and in March 2003 the government announced that it would permit the sale of several tons of transgenic soybeans that had been illegally grown in Brazil.<sup>158</sup> Additionally, Mexico has barred transgenic corn for years, and yet transgenes have entered the traditional corn varieties in remote areas of Mexico, hitherto undetected.<sup>159</sup> If pharm crops go international, it is not clear how containment will be achieved, or how shipments of food grain contaminated with pharm grain would be detected. When the international angle is factored in, even perfect containment of pharm crops in the U.S. may not be sufficient to achieve the desired assurance that these plants are not entering the food supply.

## **F. Critique of Containment Measures**

As these examples make plain, the containment measures used so far in the U.S. and Canada have not been effective at limiting the flow of transgenes. The containment measures proposed for use with pharm crops are quantitatively but not qualitatively different. The permit conditions proposed by APHIS for pharm crops will involve greater restrictions on distance between pharm crops and normal crops, and greater restrictions on harvesting and storage methods.<sup>160</sup> All of the containment mechanisms are heavily dependent on the appropriate behavior of regulated parties.

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<sup>157</sup>Mike Kepp , *Brazilian Ministry to Crack Down On Experimental Transgenic Farms*, INTERNATIONAL ENVIRONMENT NEWS, BNA Volume 24:15, July 18, 2001.

<sup>158</sup>*Brazil to allow export of GM soy despite domestic ban*, FINANCIAL TIMES , March 10, 2003.

<sup>159</sup>Ellstrand 2003, *supra* note 83, at 1773.

<sup>160</sup>Field Testing, *supra* note 61, at 11338.

Several critiques may be leveled at these containment measures. First, each of these measures leaves open the possibility of human error. It is not difficult to imagine that bagging of corn tassels could be done incompletely or not within the appropriate temporal offset period. It also easy to imagine that harvesting machinery could be slipped off the “pharm” and used in a different field. Increased enforcement, as proposed by APHIS, would presumably help, but again it is a quantitative improvement. As demonstrated in the ProdiGene and StarLink incidents, farmers and manufacturers do not always, and perhaps cannot always, be expected to abide by the permit requirements.

A second critique has to do with the probabilistic nature of these constraints. The APHIS permit requirements for pharm corn note that the one mile perimeter requirement proposed for pharm corn is eight times the 660 foot requirement set by AOSCA for maintaining seed purity.<sup>161</sup> However, the AOSCA standard is not designed to prevent all pollen drift, merely enough to retain the 0.1 to 0.5 percent purity standards.<sup>162</sup> As noted by Eastham, weather conditions can have significant effects on pollen drift for some plants, as can insects.<sup>163</sup> None of the studies reviewed addressed the issue of extreme environmental conditions, such as tornadoes, floods or unusual insect populations. Yet over a span of sufficient years, there is little doubt that a pharm crop would encounter one or more of these situations. The proposed one mile separation of pharm corn from other corn may decrease the probability of commingling, but it is easy to imagine fairly common occurrences that could compromise the containment system.

Even at a low level escape rate, plants have the possibility of self-replication and propagation. This property of living organisms raises the specter of irreversibility. It is not clear how easily even a small-scale escape

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<sup>161</sup>*Id.*

<sup>162</sup>AOSCA, *supra* note 114, at 150.

<sup>163</sup>Eastham, *supra* note 134, at 37.

of a pharm plant could be controlled. After the StarLink release was reported, Aventis CropScience, USDA and many other farmers and corporations initiated a program to eliminate StarLink from the human food chain, with early estimates of control expenses nationwide put at over \$1 billion.<sup>164</sup> This has proven to be quite difficult. As of 2003, traces of the StarLink transgenes are still detected in batches of corn slated for export. From October 2000 through March 2003, corn mills have tested over 200,000 lots of corn for StarLink, initially showing a 1.2 percent positive test rate, trending downwards to about 0.1 percent by 2003.<sup>165</sup> USDA tests continue to show batches positive for StarLink at somewhat higher rate, just under one percent.<sup>166</sup> As a single datapoint on the subject of reversibility, the StarLink experience urges great caution. Were a harmful pharm crop to escape into the food supply, the effects would be likely to linger for years.

One difficulty with physical containment is that once a plant has breached the containment, control can not easily be reasserted. As the Union of Concerned Scientists noted, a farmer that believes himself to be dealing with non-engineered crop varieties will not perform the containment techniques.<sup>167</sup> Any escape from physical containments has the possibility of spreading further and leading to increasing year-on-year contamination of the food supply.

## G. Alternative Containment Systems

A variety of biological containment systems have been proposed and tested. As opposed to the physical and

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<sup>164</sup>Barboza, *supra* note 6.

<sup>165</sup>Chris Clayton, *StarLink corn still shows up*, OMAHA WORLD-HERALD, July 30, 2003.

<sup>166</sup>*Id.*

<sup>167</sup>Mellon, *supra* note 113, at 37.

farmer-based containment systems discussed above, most biological containment systems have the appealing feature of being self-perpetuating. For example, the progeny of a plant engineered to have reduced fertility may retain that trait even after an initial escape event.

In one biocontainment approach, biologists have attempted to develop plants with limited abilities to outcross with other plants. This type of technology has been reviewed by several authors recently.<sup>168</sup> <sup>169</sup> The most widely discussed of these technologies is the so-called “terminator” technology. Essentially, a plant is engineered such that the transgene encoding the pharmaceutical product is closely linked to a transgene that causes sterility.<sup>170</sup> These technologies are referred to as “Genetic Use Restriction Technology” or “GURT” because they were originally used by companies such as Monsanto to prevent farmers from violating patent rights by retaining engineered seed for reuse in subsequent seasons.<sup>171</sup> Farmers objected to the use of these technologies in food seeds because it prevented farmers from saving seed for use in the following year.<sup>172</sup> In the context of plants designed to express pharmaceutical products, this level of control is desirable and unlikely to provoke any outcry from farmers. However, the National Research Council has noted that the GURT technology is new and not widely used in the field, and accordingly, the degree of containment achieved through GURT technology has not been established.<sup>173</sup> A similar approach involves male sterility, meaning that the plant is bred or engineered so that it will not produce pollen. This approach has been used commercially in glufosinate-tolerant canola.<sup>174</sup> However, the NRC writes, “Most types of male sterility are leaky, so it will be important to test the reliability of this trait in a representative range of environmental

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<sup>168</sup>Henry Daniell, *Molecular Strategies for Gene Containment in Transgenic Crops*, NATURE BIOTECHNOLOGY, June 2002, at 581.

<sup>169</sup>National Research Council, *Biological Confinement of Genetically Engineered Organisms* Committee on the Biological Confinement of Genetically Engineered Organisms, NATIONAL RESEARCH COUNCIL ON SCIENCE AND ENVIRONMENT, NATIONAL ACADEMIES PRESS (WASHINGTON, D.C. 2003), at 65-129.

<sup>170</sup>Daniell, *supra* note 168, at 583.

<sup>171</sup>*Id.*

<sup>172</sup>NRC 2003, *supra* note 169, at 74

<sup>173</sup>*Id.*

<sup>174</sup>Daniell, *supra* note 168, at 583.

conditions.”<sup>175</sup> Daniell also reports that male sterility techniques are seldom perfect.<sup>176</sup>

Traditional breeding techniques have been used to create sterile hybrid plants and plants that are sterile by virtue of increased numbers of chromosomes (“sterile triploids”).<sup>177</sup> Sterile hybrids need to be regenerated year after year by mating the fertile parents. Sterile triploids self-fertilize allowing propagation, but also meaning that volunteer plants would still be a risk.<sup>178</sup> The NRC reports that some sterile hybrids are fully sterile and could be used for effective biocontainment, but that sterile hybrids have not been generated for all plant types.<sup>179</sup> Triploid plants show promise but have not been fully tested for confinement possibility.<sup>180</sup> A maternal inheritance technique for transgene containment has been developed by incorporating transgenes into the chloroplast genome. A plant has several intracellular repositories for genetic material. The primary plant genome resides in the nucleus and is distributed into both female and male gametes (i.e., ovule and pollen).<sup>181</sup> However, the chloroplasts contain their own repository of genetic material, and chloroplasts are generally inherited only through the mother plant, meaning that transgenes contained in the chloroplast are not usually transmitted through the pollen.<sup>182</sup> The NRC refers to this approach as “potentially powerful” but also states, “the leakiness of the system will need to be demonstrated empirically on a case-by-case basis.”<sup>183</sup>

In summary, biological containment systems are mostly still in development, with few field tested to a point to have the full confidence of the NRC. Nonetheless, some sterile hybrids with a near-zero escape risk may

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<sup>175</sup>NRC 2003, *supra* note 169, at 78.

<sup>176</sup>Daniell, *supra* note 168, at 584-85.

<sup>177</sup>NRC 2003, *supra* note 169, at 68-70.

<sup>178</sup>*Id.*

<sup>179</sup>*Id.* at 69.

<sup>180</sup>*Id.* at 70.

<sup>181</sup>Daniell, *supra* note 168, at 581-82.

<sup>182</sup>*Id.*

<sup>183</sup>NRC 2003, *supra* note 169, at 80-81.

be available for use.

A simpler approach to preventing the flow of pharmaceutical genes into food plants is to restrict the technology to non-food plants. Plants such as tobacco, cotton and *Arabidopsis thaliana* are not used for food and are readily amenable to genetic engineering.<sup>184</sup> The level of certainty provided by this type of containment is absolute. There is no reason to believe that transgenes from one of these plants will appear in food crops.<sup>185</sup>

Pharming companies have focused on food crops. Food crops are often more heavily studied and methods for genetic manipulation have been developed. Apparently there is evidence that corn and other seed crops are particularly desirable for producing certain pharmaceutically active proteins. ProdiGene uses corn preferentially, having also tested tobacco, and notes that protein stability and shelf-life are improved for proteins expressed in corn.<sup>186</sup> Nonetheless, the non-food plant approach has been suggested by many observers, and provides the only certain approach to confinement.

This section illustrates that biological containment systems, while an appealing approach, are not yet perfected. Failsafe systems that are available, such as the use of sterile hybrids or non-food plants, limit the choice of plant available to those developing pharm plants. Thus, failsafe biocontainment will place a heavy burden on the technology, while partially effective containment systems are more widely applicable and place a somewhat lesser burden.

### III. Assessing Risks

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<sup>184</sup>Ellstrand 2003, *supra* note 83, at 1773.

<sup>185</sup>*Id.*

<sup>186</sup><http://www.prodigene.com/0202.htm>

Forcing agricultural biotechnology companies to adopt fail-safe biological containment approaches may seriously impair or delay the technology. It is a typical situation of costs and benefits. Yet under the present regulatory system, there is no mechanism for developing the information that would be needed to evaluate the benefits, the risks avoided through improved containment. The preceding discussion establishes that physical and farmer-dependent containment methods are unlikely to prevent the eventual escape of pharm plants into the food system or the environment, it does not address the matter of consequences. What harm would result upon such an escape?

As explained by the National Research Council, risk analysis is a complex field unto itself, but at a basic level most risk analysis methods involve a mathematical combination of an identified hazard and the likelihood that the hazard will occur (commonly referred to as the “exposure”).<sup>187</sup> At a crude level, an agency conducting risk analysis might provide a hazard score, measuring the degree of severity of the hazard, an exposure score, reflecting the probability that a hazard will occur, and multiply these numbers to arrive at a risk factor. The magnitude of this risk factor may then be used to guide regulatory decisions and to assess the degree of regulatory effort that is warranted.

In this section I evaluate the hazards posed by pharm plants under the assumption that they will escape confinement and enter the environment and the food supply. I also evaluate whether it is possible to assess these hazards confidently, or whether there is a significant likelihood that predictive exercises are futile. Presumably if pharm plants would pose no hazards upon escape, there would be no need for confinement. On the other hand, if a pharm plant poses a serious and highly predictable hazard, then extreme confinement or a complete ban might be the appropriate response. If science provides no predictive tools of any value,

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<sup>187</sup>NRC 2002, *supra* note 7, at 54.

than a pre-market assessment is futile and should be abandoned.

Experts have identified various hazards associated with transgenic plants, and these may be broken into three broad categories: (1) threat to food safety resulting from commingling between non-food and food plants; (2) threat of harm to natural ecosystems, primarily resulting from gene transfer from transgenic plants to wild relatives; (3) threat of economic harm and harm to agricultural practices, primarily resulting from a lack of acceptance of transgenic plant technology.<sup>188</sup>

In this section, I evaluate the degree to which the food and environmental safety risks posed by pharm plants can be predicted at present and how these predictions might be used to guide management strategies for pharm plants. I leave to the side the issue of consumer preference.

### **A. Food Safety**

In considering the area of food safety, FDA has indicated the overall policy goal of safety and nutritional assessment should be to “establish that the new food is as safe as foods in our grocery stores today.”<sup>189</sup> A key concept behind this statement is the notion that food does have risks, and there is no reason to expect that crops should be safer than other foods. FDA has noted that products such as legumes and potatoes contain toxicants that, if not removed through proper food preparation, can have human health consequences.<sup>190</sup>

The emphasis of this analysis is to establish whether FDA can, through pre-market review, evaluate whether

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<sup>188</sup>*Id.* at 245-46.

<sup>189</sup>Center for Food Safety and Applied Nutrition, *FDA's Policy for Foods Developed by Biotechnology*, Food and Drug Administration, 1995. Accessed at [vm.cfsan.fda.gov/lrd/biopolicy.html](http://vm.cfsan.fda.gov/lrd/biopolicy.html).

<sup>190</sup>Statement of Policy, *supra* note 23, at 22987.

pharm plants that are not intended for food but nonetheless enter the food supply present risks in excess of those presented by normal food crops. If FDA can provide an effective risk profile based on pre-market review, then pre-market review should be adopted as a key tool in determining the appropriate containment measures to be prescribed for each new pharm plant. A secondary consideration of this analysis is to determine whether, as a group, pharm plants raise particular health concerns.

FDA has identified the primary risks associated with transgenic plants. These risks include alterations in the nutritional content of the transgenic plants, outright toxicity of the proteins or other products produced because of the transgene, and allergenicity of the proteins expressed from the transgene.<sup>191</sup> For transgenic plant engineered to produce non-food products, such as pharm plants, the focus is on toxicity and food allergy.<sup>192</sup>

There is good reason to believe that plants producing pharmaceutical agents as a group pose an elevated risk of having toxic or other undesirable effects, although each plant is likely to have very different properties and must be analyzed on a case-by-case basis. Pharmaceutical products are, by design, usually intended to have effects on human physiology at relatively low levels. In addition, pharming technology emphasizes the yield of active pharmaceutical agent that can be obtained from a plant. An entire food batch manufactured from a pharmaceutical crop may deliver a significant dosage to a consumer. Depending on the potency of the drug, even low level contamination, as would be expected from mingling caused by pollen drift, for example, might deliver a dose that is sufficient to have undesirable effects. Proteins produced for industrial purposes may also have significant effects on human physiology<sup>193</sup>, although since this is not a primary purpose of an

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<sup>191</sup> *Id.*

<sup>192</sup> *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*, 67 FR 50578 at 50579, OSTP, August 2, 2002. Nutritional effects are presumably unimportant in pharm plants or other plants that would enter the food supply only through chance, or “adventitious” events because these plants will not become a staple dietary item.

<sup>193</sup> For example, corn producing the protein avidin has been produced for years by ProdiGene under the APHIS notification procedure. Avidin binds very tightly to a vitamin, biotin, and prolonged consumption of avidin in the diet can lead to a vitamin

industrial protein, there will be considerable variation from protein to protein. One may safely say, however, that proteins produced for pharmaceutical purposes will have effects on human physiology.

The primary route of unintentional exposure to pharmaceutical crops is oral. It is difficult to imagine that such crops would be injected into people. Inhalation is reportedly a risk for agricultural workers, but not for the general public.

By contrast, the expected route of administration for most protein drugs is not oral administration. Most proteins are degraded in the gut by a combination of stomach acids and digestive enzymes. This degradation is sufficient to render most protein therapeutics inactive. For this reason, most protein therapeutics produced today are administered intravenously. However, many of the pharmaceutical plants in development are designed explicitly for oral administration. ProdiGene has developed and patented a number of vaccination methods that involve expressing the protein for use as a vaccine in a plant and then achieving vaccination by administering plant material to a person or animal.<sup>194</sup> The plants that nearly entered the food supply in the ProdiGene incident were designed to provide an oral vaccine for swine.<sup>195</sup> ProdiGene also plans to develop corn-based human vaccines for hepatitis B.<sup>196</sup>

The use of food plants to produce orally active pharmaceutical agents should be viewed as a very serious hazard indeed because the intended mode of pharmaceutical administration and the likely mode of unintended consumption are identical. Vaccination programs using hepatitis B surface antigen are probably safe, but continued concern about side effects can be found in the literature.<sup>197</sup> Side effects do commonly result from vaccines. The decision to vaccinate a population is based on a careful epidemiological assessment of the

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deficiency. NRC 2002, *supra* note 7, at 180-181.

<sup>194</sup> See U.S. Patent Nos. 6,034,298 and 5,914,123.

<sup>195</sup> Burns, *supra* note 79.

<sup>196</sup> <http://www.prodigene.com/0302.htm>.

<sup>197</sup> See M. R. Geier, D. A. Geier DA and A. C. Zahalsky, *A review of hepatitis B vaccination*, EXPERT OPIN DRUG SAF., March, 2003, 113-22. It should be noted that concerns relating to any vaccine may derive more from the preservatives used in the vaccine. To the extent that this is the case, one could imagine safety advantages for vaccines delivered in edible food.

benefits to derived from disease protection against the number of bad outcomes expected.<sup>198</sup> A widespread food contamination with an oral vaccine plant could upset this careful balancing.

On balance, there are reasons to believe that most pharm plants will have little toxic effect on humans. Yet at the same time, certain varieties may present special risks. The key question is whether FDA is likely to be able to provide a strong predictive assessment of these risks.

FDA does have established methodologies for evaluating the toxicity of proposed food additives, and other substances that may be present in foods. This includes the analysis of animal feeding experiments, and where appropriate, human feeding experiments.<sup>199</sup> FDA has elaborate guidelines for assessing toxic properties of proposed food additives.<sup>200</sup> In addition, FDA has set up specific guidelines for evaluating the safety of proteins added to foods.<sup>201</sup> In addition, FDA maintains a list of enzyme preparation used in foods, listing over 30 types of enzymes.<sup>202</sup> To the extent that the novel non-food products found in pharm plants are also proteins, there is little reason to expect that the FDA's safety assessment system for proteins would be any less effective with these plants.

Food allergies present the primary source of uncertainty in evaluating the safety of a pharm plant. In 1992, FDA expressed concern about the transfer of proteins from a known allergenic material, such as peanuts, fish, and eggs, to a previously non-allergenic crop. An individual who is allergic to peanuts might unwittingly consume a different food item engineered to express a peanut protein and suffer an allergic reaction.<sup>203</sup> In fact, a soybean engineered to express a protein from brazil nuts was found to cause allergies in individuals

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<sup>198</sup> *Id.*

<sup>199</sup> FDA Policy, *supra* note 189, at 4. See also Office of Food Additive Safety Redbook, *Toxicological Principles for the Safety Assessment of Food Ingredients*, FDA, November 2003.

<sup>200</sup> *Toxicological Principles*, *supra* note 199.

<sup>201</sup> Office of Food Additive Safety, *ENZYME PREPARATIONS: CHEMISTRY RECOMMENDATIONS FOR FOOD ADDITIVE AND GRAS AFFIRMATION PETITIONS*, Center for Food Safety & Applied Nutrition U.S. Food & Drug Administration, January 2001.

<sup>202</sup> Office of Food Additive Safety, *Partial List Of Enzyme Preparations That Are Used In Foods*, Center for Food Safety & Applied Nutrition U.S. Food & Drug Administration, July 2001.

<sup>203</sup> Statement of Policy, *supra* note 23, at 22987.

with a Brazil nut sensitivity.<sup>204</sup> This incident validates the concept that allergenicity may be transferred from plant to plant by genetic techniques. However, it also illustrates the relative ease with which this type of allergic risk can be evaluated by testing in the sensitive population.

A second allergic risk arises from the presence of a non-food protein found in food, as would be the case for many pharm plants. Most allergies are caused by proteins, and thus the presence of a non-food protein in food raises concern. Furthermore, because there has been no food allergy experience with a non-food protein, there will not be a known sensitive population in which testing can be conducted. In 1992, FDA stated, “At this time, FDA is unaware of any practical method to predict or assess the potential for new proteins in food to induce allergenicity.”<sup>205</sup> This conclusion was reiterated in 1995 after the conclusion of a multi-agency conference on the subject.<sup>206</sup> FDA did note that allergic reactions are caused by a small subset of proteins, and that some assessment of the risk posed by a new protein could be obtained by a careful comparison to known allergenic proteins.<sup>207</sup> Another concern with allergies generally is that they may occur extremely low protein levels and may occasionally have serious health consequences, such as anaphylaxis.<sup>208</sup> During the StarLink incident, the Scientific Advisory Panel commissioned by EPA to assess the allergenicity of the Cry9C protein was unable to reach a scientifically sound conclusion on the issue.<sup>209</sup> The well-respected scientific journal *Nature Biotechnology* commented on the StarLink incident, saying, “The adventitious presence of Starlink in tacos had no consequences for human health, but could the same be said of a crop variety designed for biopharmaceutical production?”<sup>210</sup>

To conclude, in the area of food safety, FDA has many systems in place that would allow a predictive risk

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<sup>204</sup>*Safety Assurance of Foods Derived by Modern Biotechnology*, Center for Food Safety and Applied Nutrition. July 1996.

<sup>205</sup>Statement of Policy, *supra* note 23, at 22987.

<sup>206</sup>Safety Assurance, *supra* note 204.

<sup>207</sup>*Id.*

<sup>208</sup>*Id.*

<sup>209</sup>SAP Report No. 2000-01A, *Food Allergenicity of Cry9C Endotoxin and Other Non-digestible Proteins*, June 29, 2000, at 8.

<sup>210</sup>*Going with the flow*, *NATURE BIOTECHNOLOGY*, June 2002, at 527.

assessment. The problem of food allergies presents the primary source of uncertainty. While this risk might be predictable where the transgene is derived from a substance that is a known allergen, there is little predictive power for proteins from a non-food source.

## **B. Environmental Safety**

Hazards to the environment are poorly understood. The National Academy of Sciences has reviewed the issue of environmental threats posed by transgenic plants, and has stated, “[S]cientifically defensible ex ante risk assessment is not yet possible, so it will not be possible to develop a science-based trigger based solely on predictions of the risks associated with particular crop varieties.”<sup>211</sup> The most commonly cited hazard is the development of “superweeds”, wild weeds that hybridize with transgenic crop plants and acquire transgenes that make the weeds more difficult to control.<sup>212</sup> One can imagine that a weed acquiring resistance to the herbicide glyphosate would become something of a “superweed” for farmers seeking to use glyphosate as a herbicide. Any transgene designed to improve an agronomic property of a crop plant has some probability of conferring an advantage on weeds. Resistance to the European corn borer, salinity tolerance, drought resistance, all could be taken up by weeds and make the weeds more difficult to control. As noted above, there are serious weeds that cross-hybridize with agricultural varieties. Most notably, Johnson grass is considered by some to be “the world’s worst weed”, and gene flow from sorghum to Johnson grass has been observed.<sup>213</sup> There has been a reported rise in the incidence of glyphosate resistant weeds.<sup>214</sup> Glyphosate resistant weeds

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<sup>211</sup>NRC 2002, *supra* note 7, at 253.

<sup>212</sup>C. Neal Stewart, Matthew Halfhill and Suzanne Warwick, *Transgene Introgression from Genetically Modified Crops to their Wild Relatives*, NATURE REVIEWS: GENETICS Oct., 2003, at 807.

<sup>213</sup>*Id.* at 812.

<sup>214</sup>Emily Geresema, *Scientists Worry About Weed Resistance to Popular Herbicide Roundup*, ASSOCIATED PRESS, Sept. 13, 2003. Accessed at [www.organicconsumers.org/ge/weed\\_resistance.cfm](http://www.organicconsumers.org/ge/weed_resistance.cfm).

have not yet been shown to be caused by movement of a transgene from the crop to the weed. Herbicide resistance can also occur simply from the very high selective pressure that results when farmers rely heavily on a single herbicide. In other words, a weed that naturally develops a mutation that confers glyphosate resistance will likely compete very effectively against non-resistant weeds in a field where glyphosate is routinely applied, and no flow of transgenes into weeds need be posited for this effect to occur.<sup>215</sup>

Environmentalists have also expressed concerns about the effects that transgenes may have on the environment even without moving to wild sources. In the mid-1990s, scientists reported that Bt corn was killing Monarch butterflies, an endangered species. The report was highly plausible, given that Bt toxins are generally effective against Lepidoptera, including Monarch butterflies.<sup>216</sup> Follow up research has indicated that this effect is unlikely to have a significant impact on Monarch butterfly populations.<sup>217</sup> Other concerns have been expressed about the level of Bt toxin produced in the roots of some transgenic plant varieties. The Bt toxin is reported to accumulate in the soil, and it is unclear whether there will be a deleterious effect on the soil ecosystem.<sup>218</sup> Another possibility, analogous to the herbicide resistant plants is the pesticide resistant insect. In fact, Bt resistant insects have been reported, raising fears that the Bt toxin will decline in effectiveness.<sup>219</sup> Farmers do not want to enter an arms race similar to that seen in the area of antibiotics, where bacteria are developing resistance to many of the widely used antibiotics, forcing doctors to rely on less desirable second line antibiotics.

Possible environmental hazards caused by pharm plants cannot be ruled out. As noted by the NRC, scientists

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<sup>215</sup>NRC 2002, *supra* note 7, at 76.

<sup>216</sup>NRC 2002, *supra* note 7, at 70-75.

<sup>217</sup>Philip Dale, Belinda Clarke and Eliana Fontes, *Potential for environmental impact of transgenic crops*, NATURE BIOTECHNOLOGY, June, 2002, at 568.

<sup>218</sup>*Id.* at 569.

<sup>219</sup>*Id.* at 571.

have limited ability to predict such risks. In addition, the diversity of different proteins that may be expressed in pharm plants is likely to mean that a regulatory agency will have a difficult time performing a thorough analysis on each new transgenic plant.

## V. The Case for Monitoring: Managing the Unpredictable

Given that there are residual environmental and food allergy risks that will be difficult to assess in a pre-market review, the behavior of pharm plants and their transgenes should be monitored in the field.

The NRC conducted an assessment of the environmental risks posed by transgenic plants.<sup>220</sup> NRC concluded that pre-market testing would have limited predictive power, and that therefore a prudent post-commercialization monitoring system would be appropriate.<sup>221</sup> In support of monitoring, NRC noted that pre-market testing tends to be done on a small scale, and is therefore unable to detect subtle or low frequency events that become apparent on a larger scale; this point is equally applicable to the issue of food allergies, where it is well-known that relatively small populations tend to suffer from any one food allergy.<sup>222</sup> Furthermore, NRC noted that without any monitoring system it is impossible to verify the accuracy of assessments made in an initial risk assessment.<sup>223</sup>

In the case of pharm plants, there is an expectation that confinement systems should be designed to limit the likelihood of mixing with the food supply, but as noted above, such mixing is nearly inevitable. If there is no system in place to detect the presence of pharm transgenes, it will be impossible to determine whether

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<sup>220</sup>NRC 2002, *supra* note 7.

<sup>221</sup>*Id.* at 192.

<sup>222</sup>*Id.* at 194.

<sup>223</sup>*Id.* at 196.

any mixing has occurred. In retrospect, perhaps the most startling aspect of the StarLink story occurred at the outset. The first discovery of StarLink corn in the food supply was made by a non-profit group, not the regulatory agency, and not private industry. It does not appear that USDA or anyone involved in the cultivation or sale of Starlink corn was even trying to detect the possible flow of Starlink corn into the food chain. The permit issued by EPA did not require any monitoring of StarLink gene flow. One must assume that, but for Genetically Engineered Food Alert, the presence of Starlink corn in the food supply would never have been detected. The StarLink experience highlights a seemingly obvious principle: if there is no program to assess the spread of a transgenic crop after it is planted in the field, no one will perceive such a spread. A transgenic crop does not announce itself, and in most instances transgenic crops do not carry obvious markers that would allow one to detect their presence by visual inspection.

A monitoring system should be designed to provide a reasonable probability of detecting any movement of pharm transgenes into food crops and the food supply. The technology that would be used in such a monitoring system has already been developed. In response to the demand for transgene-free grain in Europe and Japan, the American food supply has begun to develop segregation and identity preservation systems that allow tracking of various transgenic food crops as they move from the farmer to the grain elevator and ultimately to the exporter or the processors. Recently enacted regulations in the European Union will require certification of less than one percent transgenic content in any imported grain. A number of new companies have been formed to provide agricultural genetic testing services. Thus the capability to monitor for the presence of transgene from pharm plants is already developed.

The NRC acknowledged that monitoring can be prohibitively expensive<sup>224</sup>, and the U.S. food industry has made a similar complaint with respect to the new EU requirements. A monitoring program intended to

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<sup>224</sup>*Id.* at 192.

prevent the undetected movement of pharm transgenes need not be as comprehensive as an industry-wide identity preservation system. Periodic checks in the vicinity of field test sites may be sufficient. Additionally, government agencies may be able to assist in developing and implementing a monitoring system, although decisions about what party should bear the cost of regulation is a matter of legislative policy. Government agencies were instrumental during the StarLink incident. EPA was able to work with private companies to develop tests for the Cry9C gene and protein. Grain Inspection, Packers and Stockyards Administration (GIPSA) developed a “dipstick” test for rapid use by parties involved in the movement and storage of corn, and particular for those needing to certify GM-free status for export. GIPSA announced in 2002 that it would begin a voluntary testing program for transgenic grains.<sup>225</sup> GIPSA has developed a variety of testing protocols for transgenic grains and conducts a validation program whereby laboratories that offer tracking services can evaluate their accuracy through a GIPSA program.<sup>226</sup> The cooperation of government and private entities should facilitate an efficient monitoring program.

The Guidelines issued by FDA, EPA and USDA recommend at least minimal efforts to facilitate detection of engineered plants. The Guidelines suggest that bioengineered pharmaceutical plant lines be designed so as to have an altered appearance relative to food plants, listing strategies such as novel colors or leaf patterns or including auxotrophic markers that could be used to identify the transgenic plants under specific growth conditions.<sup>227</sup> The guidelines also say, “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.”<sup>228</sup>

These recommendations should be made mandatory, where possible.

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<sup>225</sup> Jeffrey Fox, *US federal agencies add extra steps for handling GM plants*, NATURE BIOTECHNOLOGY, September 2002, 862.

<sup>226</sup> *Id.*

<sup>227</sup> Draft Guidelines, *supra* note 33, at 9.

<sup>228</sup> *Id.* at 9-10.

Lastly, a monitoring system would provide data with regards to the effectiveness of containment systems. If relatively simple containment systems prove, over a span of years, to be completely effective, it may be possible to scale back on other aspects of premarket safety review and resort only to the validated containment system coupled with the monitoring.

A carefully designed monitoring program will function to alert authorities to the inappropriate spread of transgenes, provide information on the effectiveness of different containment measures, and help detect and manage unexpected events.

## **VI. A New Regulatory System for Pharm Plants**

The present regulatory system is not well-suited to manage the risks associated with pharm plants. The present system depends solely on mandated containment requirements, although individual developers may seek the benefit of a voluntary FDA review. However, the optional nature of that review means that FDA is unlikely to demand or receive the same quality of information. The experiences with first generation transgenic plants and the ProdiGene plants demonstrate that physical and farmer-dependent containment systems are not reliable, and some level of commingling with the food supply is quite likely. Furthermore, it is unclear how such commingling will be detected, apart from the occasional inspections made by APHIS agents. While inspections may be effective, there is no plan for monitoring the presence of pharm transgenes in crops and grain elevators in regional proximity to the pharm crops. Therefore it will be impossible, under the present system to determine whether pharm crops and genes have entered the food supply. Even worse, if people begin to evince unusual illnesses, it will be nearly impossible to trace those symptoms to a pharm plant or transgene.

An improved regulatory structure would include the following features:

1.

A pre-market review of each new pharm plant<sup>229</sup> with respect to food safety and environmental safety;

2.

A permitting process that would mandate containment measures commensurate with environmental and food safety risks. Any pharm plant with an identifiably increased risk would need to have a failsafe containment system, meaning containment that would ensure no commingling with the food supply and/or wild plants, depending on the risk profile; and

3.

A monitoring system that would allow the detection of spreading pharm plants and transgenes, and that would provide baseline information that could be used to correlate unexpected events to the presence of pharm plants.

The expertise for this system is already developed. FDA would perform food safety review, much as it does for food additives. APHIS would perform the environmental assessment and conduct the permitting process, as it already does. APHIS could coordinate the monitoring program, drawing on expertise from industry and from GIPSA.

The authority to establish parts (2) and (3) is derived from the Plant Protection Act, which allows APHIS to administer a field permit program and to conduct inspections.

The authority to establish part (1) is not entirely clear. FDA could make approval of plant-grown pharmaceutical products contingent upon the developer submitting to a food safety review, however such a program, if formalized in a rule, might be beyond the scope of granted power. Alternatively, FDA could determine that pharm plants are “reasonably expected to become food” and are therefore unapproved food additives. FDA could support such a finding with the extensive body of evidence showing the ease with which transgenes move through the system. A developer might be able to avoid this type of jurisdiction by selecting a biological containment system that ensures that there is no possibility of mixing with the food supply, perhaps by electing a non-food plant. It would then be appropriate to exempt the manufacturer from FDA food safety review.

Agricultural biotechnology companies would benefit from a more stringent regulatory system. If pharm plants are approved for low level contamination in food, an incident of escape would not inevitably result in the condemnation of large quantities of food, as happened in the StarLink and ProdiGene situations. The ProdiGene and StarLink incidents have done great damage to the credibility of the transgenic plant industry as a whole. Bradley Shurdut, who leads government and regulatory affairs for biotechnology at Dow Agrosiences said, at a symposium on the subject, “We need regulations tough and we need them transparent. We have and continue to work with government to move this thing forward quickly and in a way that is comprehensive, so we are willing to raise the bar.”<sup>230</sup> The scientific uncertainty and high economic stakes associated with transgenic crops have already taken a toll on the first generation transgenic plants. Faced with impenetrable problems in assessing risk and millions of dollars at stake, many farmers and governing bodies have embraced an outright ban the open field growth of transgenic plants.

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<sup>230</sup>Pharming Symposium, *supra* note 8.

Monsanto is attempting to win regulatory approval for widespread cultivation of Roundup Ready wheat in Canada and the U.S.<sup>231</sup> This will be the first transgenic wheat to be widely grown, and industry participants are expressing great reluctance. Wheat pollen is reported to drift and outcross at distances of up to forty miles depending on the variety tested, but beyond distances of ten miles, outcrossing is a very low probability event.<sup>232</sup> A survey of North Dakota grain elevators revealed that 98% of operators were “very concerned” or “somewhat concerned” about the proposed introduction.<sup>233</sup> The Montana State Senate has considered a bill requiring that transgenic wheat will be introduced only when the grain is accepted by major customers.

In the summer of 2002, the United Nations World Food Programme projected that 7 million of Zimbabwe’s 12.5 million citizens were facing severe food shortages. Yet Zimbabwe turned away a shipment of 10,000 tons of corn from the United States Agency for International Development (USAID).<sup>234</sup> Zimbabwean officials expressed concern that the shipment contained transgenic corn, even though it was identical to grain that had been consumed in the U.S. for six years with no reported ill effects.<sup>235</sup>

In California, Marin County is considering a referendum to ban the growth of any transgenic crops within the borders.

If the industry does not heed these warning signs and push to establish a credible, highly effective regulatory system, pharm plants may likewise face outright bans, even in the United States.

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<sup>231</sup>Bringing New Technologies to Wheat: Information on the Development of Roundup Ready® Wheat. Monsanto, Inc. Accessed April 15, 2004 at [http://www.monsanto.com/monsanto/content/sci\\_tech/literature/techpubs/2003/wheat.pdf](http://www.monsanto.com/monsanto/content/sci_tech/literature/techpubs/2003/wheat.pdf).

<sup>232</sup>Van Acker, *supra* note 129.

<sup>233</sup>*Grain Elevator Operators Resist Transgenic Wheat*, April 16, 2003. Reported by Organic Consumers Association and accessed at [www.organicconsumers.org/wheat/transgenic\\_wheat.cfm](http://www.organicconsumers.org/wheat/transgenic_wheat.cfm). 317 grain elevators were surveyed, 52 responses were received.

<sup>234</sup>Andrew Meldrum, THE GUARDIAN, June 1, 2002.

<sup>235</sup>*Id.*