Consuming (F)ears of Corn: Public Health and Biopharming

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I'm convinced that physical containment is overrated and, while reassuring to the psyche, is hardly the line of defense one would like to put the greatest reliance upon"[2]

So what you have to keep asking yourself is: Suppose the worst happens, what are the consequences?[3]

We have entered the biotech century. Advances in biotechnology[4] are already transforming medicine, agriculture and industry in ways undreamt of thirty years ago, and the pace of scientific advances can only be expected to accelerate. Just as the industrial revolution completely transformed the era of craft and guild production, the world that biotechnology produces may be all

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[1]Visiting Professor, Michigan State University Detroit College of Law. I would like to thank B. Allen Schulz for his feedback and support, and Dean Phil Peters from the University of Missouri College of Law-Columbia for suggesting the project to me.

[2]Letter from Dr. Paul Berg to Dewitt Stetten, Chair of the NIH Advisory Committee Concerning Recombinant DNA Technology, described in M. Rogers, BIOHAZARD 151 (1977) (reflecting on the lax adherence to safety protocols for biotechnology research).

[3]Robert B. Shapiro, former CEO and Chair of Monsanto, Inc., quoted in Michael Specter, *The Pharmageddon Riddle*, THE NEW YORKER (April 10, 2000).

[4]Article II of the Convention on Biological Diversity defines biotechnology as "any technological application that uses biological systems, living organisms or derivatives thereof to make or modify products or processes for specific use." Convention on Biological Diversity, available at http://www.biodiv.org/convention/articles.asp. The United States defines biotechnology as "the use of modern scientific techniques, including genetic engineering, to improve or modify plants, animals, and microorganisms." Department of State, Frequently Asked Questions About Biotechnology, available at: http://usinfo.state.gov/gi/global_issues/biotechnology/biotech_faq.html. The State Department and USDA also provide useful glossaries of biotechnology available at: http://usinfo.state.gov/journals/ites/0903/ijee/glossary.htm and http://www.ers.usda.gov/Emphases/Harmony/issues/genengcrops/terms.htm (unfortunately the term "biopharming: is not on these otherwise useful lists, but explanations for many other terms used in this paper can be found there.) The USDA site also refers users to the more complete FAO Glossary of Biotechnology for Food and Agriculture which defines biopharming as: "the use of genetically transformed crop plants and livestock animals to produce valuable compounds, especially pharmaceuticals." http://www.fao.org/biotech/find-formalpha-n.asp. The biotechnologies discussed in this article are all rooted in insights developed through molecular biology and genetics.

but unrecognizable from today's vantage point.[5]

One of the most controversial and exciting prospects of biotechnology is biopharming–a process in which plants are genetically modified so that they endogenously produce specialty pharmaceutical or industrial proteins.[6] Many such crops are currently being planted in small test plots throughout the country. Once they are fully developed and approved, these biopharm crops will be grown in the same agricultural fields that are currently devoted to producing traditional agricultural crops.[7]

Biopharm companies envision a lucrative future in which agricultural fields, converted into biofactories, grow the raw materials for industrial or pharmaceutical production. Among the dazzling possibilities are plants that produce specialty industrial compounds like biodegradable plastics[8] and polyesters;[9] or drugs to treat a variety of human diseases, such as cancer, HIV, and

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[5]See generally, Chris R. Somerville, Daroi Bonetta, *Plants as Factories for Technical Materials,* 125 PLANT PHYSIOL. 168-171 (January 2001) (hereafter "*Plants as Factories*").

[6]Biopharming involves inserting novel genes into crop plants, like corn, in order to make the plants manufacture proteins that may be used as drugs, vaccines, enzymes, antibodies, hormones or industrial chemicals. Essentially biopharming converts plants into a living factory for chemical or pharmaceutical production. Although biopharming uses food crops as its production vehicle, biopharm crops are not food and are not intended for human consumption.

[7] There are generally three types of biobased products in various stages of planning or production: commodity chemicals (like ethanol or oil-based inks); specialty chemicals (pharmaceuticals and plastics) and materials (wood, paper etc.) Biobased commodity and materials production will largely be outside the scope of this article because the various proposals being floated do not typically involve plants bioengineered to express novel, non-food compounds.

[8]Henry Daniell, *Environmentally Friendly Approaches to Genetic Engineering,* 35 Cell Dev. Biol-Plant 361, 362 (1999) (citing other sources), (hereafter, *Environmentally Friendly Approaches).*

[9]*Plants as Factories,* 125 PLANT PHYSIOL. at 169, supra n. __; C. Nawrath, et. al., *Targeting the polyhydroxy-butyrate biosythetic pathways to the plastids of Arabidopsis thaliana results in high levels of polymer accumulation*, 91 PROC. NATL. ACAD. SCI. USA 12, 760-764 (1994).

Alzheimer's.[10] The allure of these crops is clear–an environmentally sustainable,[11] and inexpensive replacement for costly drugs and petrochemicals.[12]

At the same time, there are some jarring points of tension, if not outright contradiction, between widespread planting of biopharm crops and the ongoing expectation of a safe and secure food supply.[13] Biopharming frequently uses corn and other food crops as production vehicles, but these crops are emphatically **not** food and are not intended for human consumption. Biopharm crops therefore pose "a wholly different order" of environmental and human health risks.[14]

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[10]National Research Council, BIOBASED INDUSTRIAL PRODUCTS: RESEARCH AND COMMERCIALIZATION PRIORITIES, (2000)

[11]Farming already raises a whole host of environmental issues, many of which are only poorly addressed by existing environmental laws. For example, factories are point-sources and must comply with environmental statutes, including the clean air act and the clean water act. Agricultural run-off is not regulated under the CWA. Biopharm crops will require tremendous inputs of fertilizer and pesticides, and biopharm runoff will likely be a new means to introduce toxins and pollutants into the environment. Under current CWA standards, this runoff would not be regulated. It would be entirely unacceptable if agriculture became a vehicle for transferring industrial production out of environmental constraints.

[12]Indeed, biopharming has been heralded as, inter alia, a means to radically reduce the United States' dependence on foreign oil. *See e.g.*, Melvin Calvin, *New Sources for Fuels and Materials*, 219 SCIENCE 24 (Jan. 1983) (presciently speculating that gene transfer could be used to develop new fuels); for current developments in biofuels and bioenergy, *see,* The Department of Energy's National Biofuels Project, at http://www.ott.doe.gov/biofuels/.

[13]See generally, MEMORANDUM FOR THE PRESIDENT'S COUNCIL ON FOOD SAFETY (August 25, 1998), available at http://www.foodsafety.gov/~fsg/presidentscouncil.html (describing national expectations of food safety). For a typical description of the safety of the American food supply and of regulatory effort, see, Statement of Bernard A. Schwetz, D.V.M., Ph.D., Acting Principal Deputy Commissioner, Food and Drug Administration, BEFORE THE COMMITTEE ON GOVERNMENTAL AFFAIRS SUBCOMMITTEE ON OVERSIGHT OF GOVERNMENT MANAGEMENT, RESTRUCTURING and the DISTRICT OF COLUMBIA (October 10, 2001). Although biopharming raises a host of pressing environmental questions that are both significant in their own right and because of their indirect human health implications, this article focuses mostly on direct human health questions raised by the likelihood of commingling these biopharm crops with conventional crops destined for use as food or feed. Thus, many important environmental considerations are beyond the scope of this article. Similarly, the ethical questions swirling around biopharming–converting land from food production to biopharming when the FAO estimates that one in five humans are malnourished, the consolidation of agribusiness and its attendant affects on farmers and on biodiversity–will also not be discussed.

[14]National Research Council, ENVIRONMENTAL EFFECTS OF TRANSGENIC PLANTS: THE SCOPE AND ADEQUACY OF REGULATION, p. 245 (2002), hereafter "ENVIRONMENTAL EFFECTS".

Despite the unique risks, biopharm crops have been tested in fields across the country under the same laissez-faire standards used for first-generation GM crops[15]–with minimal and poorly enforced safety precautions based on physical containment. In the last decade, biotech companies and research universities have violated even those minimal safety precautions more than a hundred times.[16] Because many of these open-air field tests of experimental biopharm crops take place in the corn belt, these violations put the food supply at a high risk for contamination.[17]

Contamination of food crops with non-food, biopharm compounds is a serious threat to human safety and could result in rapid dissemination of non-food pharmaceutical or industrial compounds through the world food supply. There is no room for trial and error. Once contamination occurs it will be next to impossible to "uncontaminate" the food supply.[18] Unfortunately, important safety issues have been sidelined in order to facilitate rapid growth of this

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[15]For a description of these requirements, see Rebecca Bratspies, *The Illusion of Care: Regulation, Uncertainty and Genetically Modified Food Crops*, 10 N.Y.U. Env. L. J. 297 (2002). See also, Gregory N. Mandel, *Gaps, Inexperience, Inconsistencies, and Overlaps: Crisis in the Regulation of Genetically Modified Plants and Animals*, available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=418221.

[16]APHIS, Compliance and Enforcement, available at: http://www.aphis.usda.gov/brs/compliance.html. Although APHIS characterizes this as a low number of violations, and therefore a success story, others are far less sanguine about the conclusions to be drawn from this number. See, e.g., Academia/Industry Violated USDA Rules, available at: http://pewagbiotech.org/buzz/display.php3?StoryID=114.

[17]Indeed, in 2002, the Office of Science and Technology Policy acknowledged the significance of this risk. See, *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 Fed. Reg. 50,587 (Aug. 2, 2002) ("As the number and diversity of field tests increase, the likelihood that cross-pollination due to pollen drift from field tests to commercial fields and commingling of seeds produced under field tests with commercial seeds or grain may also increase. This could result in intermittent, low-levels of biotechnology-derived genes, and gene products occurring in commerce that have not gone through all applicable regulatory reviews.")

[18]In the context of first-generation GM crops, industry trade groups acknowledge that cross-pollination, adventitious commingling and other "causes" make it virtually impossible to assure that any United States corn shipment is 100% non-GMO. See, Value Enhanced Grain Solutions, Introducing VEG to the World Biotech Controversy, (August 22, 2002), available at http://www.vegrains.org/cgi-bin/english/Commentary%200802.cfm. Over and above any human health impacts, biopharm contamination of the food supply will likely have dramatic ramifications for the United States' share of the global commodities market.

nascent industry. First and foremost, there are readily available and far safer alternatives that could be used instead of food crops for biopharm production. But, because market forces diverge from the public's interest on this point, those safer options have not been pursued. Without government action forcing innovation towards achieving public health ends, it is clear that these options will remain unexplored. At the very least, there should be a moratorium on field testing these crops until a host of health-related questions are answered. Among the most pressing questions are: do biopharm residues bioaccumulate?[19] Is there a threshold below which these compounds can be safely consumed? Are there low-level, long-term health effects? Are these compounds allergens,[20] or toxins?[21] Are biopharmed crops anti-nutrients?[22] How persistent are these compounds in the

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[19]For this reason, opponents of biopharming refer to the practice as pharmageddon. See, e.g., Maw-Wan Ho, *Pharmageddon*, available from the Institute of Science in Society; http://www.i-sis.org/. Although this characterization is sensational, even those scientists closely affiliated with biopharm companies acknowledge that precautionary measures should be taken when biopharmaceuticals are likely to persist in the environment or bioaccumulate. See, e.g., Henry Daniell, Stephen J. Streatfield and Keith Wycoff, *Medical molecular farming: production of antibodies, biopharmaecuticals and edible vaccines in plants*, 6 TRENDS IN PLANT SCI. 219-226 (May 2001).

[20]An allergic reaction is an abnormal response of the body's immune system to an otherwise safe compound. Some reactions are life threatening, such as anaphylactic shock. Some of the biopharm products currently under development have been engineered to produce trypsin. See e.g., Howard, US Patent #6,087,558 (July 11, 2000) (claiming invention of a transgenic plant that produces trypsinogen–a precursor of trypsin). Trypsin has a history of eliciting allergic responses in exposed populations. For allergy information, see, Harvey R. Colten, *Immediate hypersensitivity to Hog Trypsin Resulting from Industrial Exposure* 292 N.E.J. Med 1050 (May 15, 1975); P. R. Shewry, et al, *Plant protein families and their relationships to food allergy*, 30 Biochem. Soc. Trans. 906 (2002)(identifying trypsin as an allergin.). The poster child for inadvertent creation of allergenic products through genetic engineering involved the experimental transfer of a brazil nut protein to soybeans. See, J.A. Nordlee, S.L. Taylor, J.A. Townsend, L.A. Thomas, and R.K. Bush, *Identification of a Brazil-nut Allergen in Transgenic Soybeans* 334 N.E. J. Med. 688-692 (1996).

[21]A toxic reaction in humans is a response to a poisonous substance. Unlike allergic reactions, all humans are subject to toxic reactions. The Codex Alimentarius considers evaluations of allergenicity, toxicity and anti-nutrient potential to be integral components of any food safety risk assessment process. Codex Principles and Guidelines on Foods Derived from Biotechnology, (prepublication), ftp://ftp.fao.org/codex/standard/en/CodexTextsBiotechFoods.pdf.

[22]Anti-nutrients are naturally occurring compounds that interfere with absorption of important nutrients in digestion. For example, avidin, the first commercialized biopharm crop has a well known ability to interfere with vitamin B absorption. Baszczynski, US Patent # 5,767,379 (June 18, 1998) (claiming invention of a transgenic plant that

soil? How toxic are they to wildlife? How likely is the prospect that these non-food compounds could be spread to wild relatives?[23]

Unfortunately, under the United States' fractured regulatory system there is no way even to pose these questions with regard to biopharm crops, let alone to answer them. Part of the problem is that no regulatory agency has a clear statutory mandate to regulate biopharming. As a result, there are no coherent overarching government policies capable of ensuring that this new technology is safely explored and exploited.[24]

The crisis is on our doorstep. According to some predictions, at least ten percent of United States agricultural lands will be devoted to biopharming by the end of the decade.[25] Thousands of nonedible and potentially harmful compounds may soon be grown in corn fields throughout the

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produces avidin) available from the ProdiGene website http://www.prodigene.com/0206.htm. See e.g., MERCK MANUAL OF DIAGNOSIS AND THERAPY, Biotin Deficiency and Dependency, available at http://www.merck.com/mrkshared/mmanual/section1/chapter3/3o.jsp; Bregola G; Muzzolini A; Mazzari S; Leon A; Skaper SD; Beani L; Bianchi C; Simonato M, *Biotin deficiency facilitates kindling hyperexcitability in rats*, 7 NEUROREPORT, 1745-8 (July 29, 1996)(inducing biotin deficiency by controlling avidin consumption); T. Watanabe, *Dietary biotin deficiency affects reproductive function and prenatal development in hamsters*, 123 J. NUTR. 2101-08 (Dec. 1993) (same);.Carey CJ, Morris JG., *Biotin deficiency in the cat and the effect on hepatic propionyl CoA carboxylase*, 107 J. Nutr. 330-334 (1977) (same). Donald M. Mock, Nell I. Mock, Christopher W. Stewart, James B. LaBorde, and Deborah K. Hansen, Marginal Biotin Deficiency Is Teratogenic in ICR Mice, 133 J. NUTR. 2519-2525 (August 2003) (same).

[23] In November 2003, a coalition of public interest groups filed suit in Hawaii district court requesting an injunction barring future biopharm field tests until these questions are answered. *Center for Food Safety v. Veneman*, complaint available at: http://www.centerforfoodsafety.org/li/BiopharmComplaint.pdf.

[24]Even BIO, an industry trade and lobbying group concedes that there is no United States policy on industrial biotechnology. *See* BIO External Resources, available at www.bio.com (Identifying four key publications that "represent, as close as you will find, a US policy on industrial biotechnology.") In 2003, APHIS published interim guidelines for industrial biotechnology. USDA, Introductions of Plants Genetically Engineered to Produce Industrial Compounds, 68 Fed. Reg. 46,434 (August 6, 2003). For the first time, these new regulations require that any such introductions be pursuant to a permit. At least 10 industrial biopharm field tests had already been conducted under a less stringent notification procedure. Id at 46,435.

[25] See e.g., Biomass Technical Advisory Committee, Vision for Bioenergy & Biobased Products in the United States, (October 2002); Aaron Zitner, *Fields of Gene Factories*, L.A. TIMES, June 4, 2001, at A1; Scott Kilman, *Food, Biotech Industries Feud Over Plans for Bio-Pharming*, WALL ST. J., Nov. 5, 2002, at B7.

country. Without detailed and enforceable standards for responsible use of this new technology, it is inevitable that these biopharm crops will contaminate crops destined for use as human food.[26] The health risks from this consuming these adulterated foods could be serious.

Nevertheless, industry and governmental regulators have failed to impose obvious biological controls that would greatly protect the public's safety, while still permitting exploitation of this technology. For example, biopharming ought not be done in food crops, or, at the very least, ought not be released into the open environment of an agricultural field (as opposed to being grown in a greenhouse) before basic research has demonstrated that there will be no negative health effects from consuming contaminated foods.[27] Instead of adopting these sensible precautions, regulators have simply assumed that contamination can be avoided through use of physical containment measures. This wildly optimistic assumption is not shared by biopharm developers who admit that biopharm proteins will likely wind up in the food supply. Moreover, physical containment measures have not shown much success in existing GM crops. [28]

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[26] Indeed, in 2003 USDA found that about 20% of farmers growing existing GM crops failed to comply with planting regulations intended to prevent contamination of conventional crops. Emily, Gersen, *USDA Survey Shows Biotech Rules Breaches*, WASHINGTON POST, Sept. 10, 2003. Given these high levels of non-compliance with existing requirements and lax regulatory oversight, there is no reason to believe that farmers' behavior will be any different with regard to biopharm crops. And evidence of contamination is mounting. For example, after just two years of Canadian cultivation, GM canola has cross-pollinated so extensively that a new, triply herbicide resistant, feral canola has emerged. Jim Orsen, *Gene Stacking In Herbicide Tolerant Oilseed rape: Lessons from the North American Experience*, English Nature Research Reports, (January 2002) available at: http://www.english-nature.org.uk/pubs/publication/PDF/enrr443.pdf. In light of these findings, any regulatory decisions about these crops must assume that commingling will occur.

[27]EPA was advised that transgenic plants producing pharmaceutical compounds be tested for their biological effects at dietary concentrations which, at minimum, are likely to be encountered in the transgenic plant itself. Mammalian Toxicity Assessment Guidelines for Protein Plant Pesticides, Scientific Advisory Panel to the EPA, SAP Report No. 2000-03B, September 28, 2000. USDA does not require any such testing before permitting biopharm crops to be field tested.

[28]Physical containment measures involve using planting distances or timing to prevent contamination of conventional crops with GM crops. Unfortunately, for existing GM crops, physical contamination measures have largely been ineffectual, either because the requirements are to lenient or because they are not being implemented. Indeed, a 2003 USDA survey found that about 20% of farms growing GM crops failed to comply with planting regulations intended to ensure physical containment. Emily Gerseney, USDA Survey Shows Biotech Rules

The limited scope of existing biopharm regulation leaves the public unprotected and exposed to an unacceptable level of risk. Moreover, the mere threat of commingling may be enough to destroy the United States' multi-billion dollar export trade in corn and other commodities.[29] These failures to address the problem of contamination and commingling become even more critical now that the Cartagena Protocol on Biosafety has entered into force.[30] Article 10 of the Protocol gives states the power to refuse import of the products of biotechnology (called living modified organisms or LMOs in the Protocol) in order to avoid or minimize adverse effects on human health or the conservation and sustainable use of biological diversity.[31] It is hard to imagine anything more likely to justify a refusal to import under the Cartagena Protocol than undetectable commingling of industrial or pharmaceutical crops containing non-food proteins with export food crops.

Protecting the public's interest in this context will require government to assume a far more active role than the hands-off attitude that has been the hallmark of conventional agricultural policy.

Breaches, Washington Post September 10, 2003.

[29] For example, the European Union has set a 1% labeling threshold for presence of approved GMOs in food. Regulation (EC) No 1139/98 as amended by Regulation (EC) No 49/2000. There is a zero tolerance level for unapproved GMOs. Corn is the United States' largest crop, typically between 9-10 billion bushels annually. See generally, Corn Refiners Association, US Corn Production, available at http://www.corn.org/web/uscprod.htm. Iowa, Illinois, Nebraska, and Minnesota alone produce more than 50 percent of the United States' corn crop. U.S. Grains Council, World Corn Production and Trade, available at http://www.grains.org/grains/corn.html. Other major corn-producing states include Indiana, Wisconsin, South Dakota, Michigan, Missouri, Kansas, Ohio and Kentucky. Id. In 2000, the United States grew 43 percent of the world's corn and is the single largest corn exporter, providing 64% of corn sold in the international corn market. Id.

[30] The text of the Cartagena Protocol on Biosafety is available at: http://www.biodiv.org/biosafety/protocol.asp . The Protocol entered into force on September 11, 2003 following the 50th ratification, by Palau. There are currently 60 members of the Protocol, including the European Union and other significant United States trading partners like Mexico. Cartagena Protocol on Biosafety, Status of Ratification and Entry into Force, available at: http://www.biodiv.org/biosafety/signinglist.aspx?sts=rtf&ord=dt.

[31] Id. Section 11.

This article raises a few of the more pressing public health questions that should be resolved before substantial portions of the nation's crop land are diverted from food production to biopharming. Part I provides an introduction to biopharming and outlines the various plans and projections for its commercial exploitation. Part II examines the existing regulatory structure, highlights some of its most critical weaknesses, and points out the serious risks this structure creates *vis-a-vis* the integrity of the food supply. Part III articulates a central conclusion that safe and successful exploitation of these new technologies will demand a markedly different regulatory regime than the *laissez-faire* system that has prevailed in conventional agricultural policy. To that end, this section proposes some alternatives that would better safeguard public health while still permitting exploration of this exciting new technology.

I. A Brief Introduction to Biotechnology

Most food crops have been modified in order to improve their agronomic and nutritional characteristics. For millennia, this process was based on trial and error, rather than any systematic understanding of the mechanisms of trait inheritance. Very early in human agronomic history it became clear that desirable agronomic traits could be accentuated by controlling plant mating. Unfortunately, for most of human agricultural history there was no way to predict the outcome of a cross between two particular parents. In 1865, an Augustinian monk named Gregor Mendel changed all that. Working with pea plants, Mendel documented that there was a predictable pattern to the appearance of heritable traits in future generations. Mendel conclusively demonstrated what are now recognized as fundamental laws of genetic inheritance.[32] He deduced that what he called "heritable factors" (now called genes or alleles) come in pairs, segregate independently and are

[32]These are the laws of heritability and independent assortment of traits. There are many good websites that explain these scientific principles in lay terms. For an excellent introduction to the basics of genetics from Mendel to modern biotechnology intended for high-school students, see, *DNA From the Beginning*, produced by Cold Springs Harbor Laboratory and available at http://www.dnaftb.org/dnaftb/. Other useful works, accessible to the non-scientist, include Robin Marantz Henig, THE MONK IN THE GARDEN: THE LOST AND FOUND GENIUS OF GREGOR MENDEL, THE FATHER OF GENETICS (2000); Matt Ridley, GENOME: THE AUTOBIOGRAPHY OF A SPECIES IN 23 CHAPTERS (2000).

governed by principles of dominance and recessiveness. These patterns of inheritance are now referred to as the Mendelian laws of genetics.

Although his paper *Versuche über Pflanzen-Hybriden* ("Experiments in Plant Hybridization")[33] went initially unnoticed in scientific circles, it would soon transform agriculture. Armed with an understanding of Mendelian patterns of inheritance, plant and animal breeders began to combine desirable traits in a much more systematic fashion. By crossing and recrossing individuals with desirable characteristics, breeders were able to create new, higher-yielding varieties of existing crops. The resulting crops were more productive and easier to grow.

The next major milestone for agricultural biotechnology dates to James Watson and Francis Crick's 1953 paper *A Structure for Deoxyribonucleic Acids* describing the structure of the DNA molecule.[34] This paper is generally considered to have ushered in the era of molecular genetics. The discovery of the chemical structure of DNA opened up new vistas in biological and biochemical research.

By the early 1970's, Stanley Cohen and Hubert Boyer had built on Watson and Crick's work by successfully splicing a gene from one organism and moving it into another–the first use of recombinant DNA technology.[35] Suddenly researchers could move genes from one species to another, thus overcoming the reproductive limits imposed by sexual incompatibility among species. Cohen and Boyer recognized the potential risks of their new technique and attempted to exercise

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[33]Both the original text and an English translation are available at http://www.mendelweb.org/MWpaptoc.html.

[34]James Watson and Fredrick Crick, *A Structure for Deoxyribose Nucleic Acid*, 171 NATURE 737 (1953). Watson and Crick were awarded the 1962Nobel prize for this discovery. For a first-hand, and somewhat scandalous account of this discovery, see James Watson, THE DOUBLE HELIX: A PERSONAL ACCOUNT OF THE DISCOVERY OF THE STRUCTURE OF DNA, 1968

[35]See e.g., Stanley Cohen, A. Chang,, Herbert Boyer, and Robert Helling, Construction of Biologically Functional Bacterial Plasmids In Vitro, 70 Proc. Nat. Acad. Sci. 3240-3244 (1973).

some control over its uses.[36]

Cohen and Boyer's concerns about the potential hazards of these new techniques mirrored similar concerns that other researchers were expressing.[37] In light of the as-yet-unassessed but potentially harmful consequences of this new research, the scientific community called for a voluntary moratorium on genetic engineering.[38] At a 1975 conference held at Asilomar Conference Center in Pine Grove, California,[39] 150 scientists from around the world met to hammer out a set of safety precautions for genetic research. Known as the Asilomar Consensus Statement, the conference recommended lifting the self-imposed moratorium and replacing it with guidelines for genetic engineering research.[40] The central assumption was that the unknown hazards of genetic engineering should be contained biologically and physically.[41] This consensus formed the basis for the Recombinant DNA Research Guidelines issued by the National Institute of Health in

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[36]Stanley Cohen, The Manipulation of Genes, SCIENTIFIC AMER. 25, 32 (Jan. 1975).

[37]See e.g., Letter from Maxine Singer and Dieter Soll to National Academy of Science and the National Institute of Medicine, reprinted as *Guidelines for Hybrid DNA Molecules,* 181 SCIENCE 114 (1973).

[38]Paul Berg, et al, *Letter from the Committee on Recombinant DNA Molecules of the National Academy of Science,* 185 SCIENCE 114 (1974).

[39]For a recent account of that historic meeting, see, Marcia Barinaga, *Asilomar Revisited: Lessons for Today?* 287 SCIENCE. 1584-1585 (March 3, 2000). See also, House Subcomm. On Science, Research and Technology, Genetic Engineering, Human Genetics and Cell Biology, DNA Recombinant Molecule Research (Supp Rept.II) 94th Cong., 2d Sess. 20, 91-99 (1976).

[40]Paul Berg et al., *Asilomar Conference on Recombinant DNA Molecules*, 188 Science 991 (1975) ("... the evaluation of potential biohazards has proved to be extremely difficult. It is this ignorance that has compelled us to conclude that it would be wise to exercise considerable caution in performing this research."; For an interesting account of the self-regulatory project, see, J.P. Swazey et al., *Risks and Benefits, Rights and Responsibilities: A History of the Recombinant DNA Research Controversy*, 51 S. Cal. L. Rev. 1019 (1978).

[41]Berg, 188 SCIENCE at 991, supra n. __. See also, Berg. et al, *Statement of the Asilomar Conference on Recombinant DNA Molecules*, 72 PROC. NATL. ACAD. SCI. USA 1981, 1982 (1975).

1976.[42]

Until 1984, these guidelines, which applied to researchers funded by NIH, were the only formal control over DNA research. A successful legal challenge to decisions made under those guidelines forced the Reagan Administration to develop a more overarching regulatory policy to guide federal decisionmaking about biotechnology research and its products.[43] To that end, the Office of Science and Technology Policy issued the Coordinated Framework for Regulation of Biotechnology.[44] The Framework purported to describe the comprehensive federal regulatory policy for ensuring the safety of biotechnology research and products.[45] The Framework announced that no new laws would be needed to respond to challenges posed by this new technology. Instead, products of biotechnology would be regulated under existing laws based on their intended use–thus food would be regulated under the Federal Food Drug and Cosmetic Act, pesticides under the Federal Insecticide Fungicide Pesticide and Rodenticide Act, agricultural plants under the Plant Protection Act, and so on.[46] One unfortunate consequence of this reliance on

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[42]See, Decision of the Director of NIH to Release Guidelines for Research on Recombinant DNA Molecules, 41 Fed. Reg. 27,902, 27,903 (July 7, 1976). The guidelines, as updated, are still applicable to research funded by NIH or conducted at NIH, 41 Fed. Reg. at 27,902, and compliance with the guidelines is a condition for continued NIH funding. *Id.* at 27,921. The 1976 guidelines prohibited six types of rDNA experiments until more could be learned, *Id.* at 27,908; allowed other rDNA experiments to proceed only under strict safety standards, *Id* at 27,909; required the physical or biological containment of rDNA recombinants in the laboratory; *Id* at 27,907; and prohibited the deliberate release of rDNA organisms into the outside environment until more could be learned, *Id* at 27,910. Peer review was the primary means to ensure that these guidelines were carried out.

[43]*Foundation on Econ. Trends v. Heckler*, 756 F.2d 143, 151 n.5 (D.C. Cir. 1985) (upholding an injunction barring deliberate release of a genetically modified organism known as "ice-minus" until NIH completed an adequate environmental impact statement.

[44] Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg, 23,302 (June 26, 1986).

[45]For a thorough description of the Framework and its development, see D. L. Uchtmann, StarLink–A Case Study of Agricultural Biotechnology Regulation, 7 Drake J. Agric. L. 159 (2002).

[46]Coordinated Framework, 51 Fed. Reg. At 23,302.

existing law has been an erosion, over time, in the commitment to biological containment measures.

During the 1980's researchers developed methods to integrate foreign DNA permanently into plant genomes, enabling the production of transgenic plants expressing a wide variety of foreign genes.[47] In a process called transformation,[48] genes coding for a specific trait can be isolated from any organism and inserted into the embryos of any food crop. The transformed embryos are then grown into adult plants. These transformed or bioengineered plants will express the newly added trait. Researchers use this technology to manipulate plants in unprecedented fashions, and, in the past decade, agricultural researchers have used these genetic foundations to sequence a series of plant genomes.[49] Information gleaned from this new technology opened up immense possibilities for agriculture and began the rapid cascade of scientific progress that I am calling "the ag-biotech revolution."

The first genetically engineered crops were commercialized in 1996, and by 2001, United

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[47]J. Schell, *Transgenic Plants as Tools to Study the Molecular Organization of Plant Genes*, 237 SCIENCE 1176-83 (1987).

[48]There are three primary means to transform, or genetically modify, plants. The most common takes advantage of the unique properties of Agrobacterium tumefaciens, a soil bacteria that infects plants by transferring a plasmid of its own DNA into the target plant. By modifying the genes contained in this plasmid, A. tumefaciens infection can be a means to deliver desirable genes into plant cells instead of the bacteria's own infective genes, which cause Crown Gall disease. Because A. tumefaciens is a known plant pest, these transformations fall neatly within USDA's regulatory authority as outlined in the Plant Protection Act, 7 U.S.C. §§ 7701-7772 (2000). By contrast, USDA authority over the other primary methods of transforming plants, the "biolistics" or "gene gun" method and electroporation are less clear. ADD DESCRIPTION. These are the various techniques that I will refer to as genetic engineering, bioengineering, genetic modification, or biotechnology.

[49]There are plant DNA libraries for over 30 important crops, See, Plant DNA Library, available at http://www.nal.usda.gov/pgdic/dnalibr/ and there are almost a hundred Plant DNA mapping projects around the world. Plant Genome Mapping Projects, available at http://www.nal.usda.gov/pgdic/Map_proj/. In 2000, the entire Arabidopsis genome (a plant widely used as a model plant organism) was sequenced. See, The Arabidopsis Information Resource, available at http://www.arabidopsis.org/.

States farmers were devoting approximately 88 million acres to GM crops[50]–the lion's share of the 130 million GM acres planted worldwide.[51] In 2003, 73% of the cotton, 81% of the soybeans and 40% of the corn planted in the United States were GM varieties.[52] Biotech research has grown at an even more explosive rate. In 1994, approximately 7,000 acres in the United States were planted with 593 biotech field tests; in 2001, there were 57,000 experimental acres planted with 1,117 field tests.[53] While most of these were field tests of first-generation GM crops (those engineered for herbicide resistance or to produce endogenous pesticides), some 300 were biopharm crops.[54]

A. Biopharming 101

During the 1990's researchers around the world embarked on the most ambitious biotechnology project ever–the sequencing of the human genome.[55] The Human Genome

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[50]OSTP, *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 Fed. Reg. 50578 (August 2, 2002).

[51]See, Bill Freese, MANUFACTURING DRUGS AND CHEMICALS IN CROPS: BIOPHARMING POSES NEW THREATS TO CONSUMERS, FARMERS, FOOD COMPANIES AND THE ENVIRONMENT (2002) available at: www.foe.org/safefoods/BIOPHARM_FACTSHEET.doc, hereafter ("MANUFACTURING DRUGS"). The increases are most dramatic in the United States, but Canada, Argentina, and China have also experienced significant growth in the development and use of biotechnology-derived crops.

[52]See, ERS, Adoption of Genetically Engineered Crops in the United States, available at: http://www.ers.usda.gov/Data/BiotechCrops/adoption.htm.

[53]OFFICE OF SCIENCE AND TECHNOLOGY POLICY, 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, 62. Fed. Reg. 50578 (Aug. 2, 2002).

[54]MANUFACTURING DRUGS at 7, supra n. __. Between 1989 and July 2003, APHIS considered 170 permit applications–162 permits were issued, seven were withdrawn and one is still pending. No applications were denied.

[55]A complete sequence of the human genome was announced in April of 2003. See, www.genome.gov.

Project[56] and related biomedical research has spawned a generation of highly specialized drugs based on antigens (vaccines), recombinant proteins (biologics) and human antibodies (collectively "therapeutics"). Demand for therapeutics is growing rapidly, especially those designed for chronic illnesses like psoriasis, allergic asthma, and rheumatoid arthritis. Meeting the projected demand for these therapeutics will require thousands of kilograms of purified proteins.[57]

Commercial production of these products currently relies on abiotic fermentation (primarily in *E.coli* or yeast) or on mammalian cell culture (primarily in Chinese hamster ovary cells "CHO").[58] These expression systems have some serious drawbacks: they tend to be expensive, labor intensive, and they produce relatively low yields that fall short of supplying all patients in need. Generally, recombinant mammalian systems can produce about 1-4 grams of a therapeutic protein/litre of media every 2-3 weeks,[59] while recombinant E. coli systems yield 1-4 grams/liter every 1-2 days. Recombinant monoclonal antibody culture in Chinese hamster ovary (CHO) cells yields .5-1 gram/liter per day, and mammalian cell perfusion bioreactor systems yield about .3 gram/liter each day. Biopharming represents the cutting edge of the research on increasing yields with at least 120 different research institutions currently developing a staggering array of biopharm products.[60]

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[56]Information about the human genome project is available at http://www.science.doe.gov/ober/hug_top.html.

[57]Stephan Herrera. *Protein Therapy Could Heal Agbio*. Red Herring (September 15, 2001) available at http://www.agbioworld.org/biotech_info/articles/interviews/protein_therapy.html.

[58]Cramer, *Transgenic Plants for Therapeutic Proteins* at __, supra n. __.

[59]All of the production figures in this paragraph come from Ronald A. Rader, BIOPHARMA: Biopharmaceutical Products in the U.S. Market, 2nd Ed. (2003), p. 17.

[60]APHIS, Introduction of Plants Genetically Engineered to Produce Industrial Compounds, Interim Rule, 68 Fed. Reg. 46,434 (August 6, 2003) (indicating that roughly half of the entities are private companies and half are research institutes) hereafter "Interim Rule".

At least in theory, plants can be engineered to express high levels of the desired pharmaceutical protein.[61] One 200-acre biopharm field could therefore produce significantly greater quantities of therapeutics than current methods. Moreover, biopharm crops offer some other distinct advantages for producing pharmaceutical proteins. Large-scale biopharming of these compounds should be more economical than current production techniques that rely on mammalian cell cultures, because the capital investment costs are relatively low (no need to build high-tech facilities).[62] Some estimates indicate that biopharming could reduce production costs for these therapeutics by an order of magnitude.[63] Biopharming can also draw on a wealth of existing agronomic experience with growing, harvesting and processing these crops in their conventional forms. Unlike CHO or *E. coli* production techniques, biopharming does not require a highly educated and tech-savvy workforce. Biopharmed therapeutics may also be safer than those produced via existing techniques, because plant-produced therapeutics have a reduced risk of carrying human pathogens.[64]

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[61]For example, avidin is expressed at 1.5-3% of total soluble protein in corn seeds, Elizabeth E. Hood, et al, *Commercial Production of avidin from transgenic maize: characterization of transformant, production, processing, extraction and purification*, 3 MOLECULAR BREEDING 291, 292 (1997). Chloroplast transformation could potentially increase that yield by an order of magnitude. See, Darnell, *Environmental Friendly Approaches*, supra n. __.

[62]Stephen J. Streatfield, et al, *Plant-based vaccines: unique advantages* 19 VACCINE 2742-2748 (2001); Takeshi Arakawa, et al, *Expression of cholera toxin B subunit oligomers in transgenic potato plants*, 6 TRANSGENIC RESEARCH 403, 412 (1997) (describing biopharming as safer and more cost effective).

[63]MANUFACTURING DRUGS at 7, supra n. __; *see also*, James W. Larrick, Lloyd Yu, Clarissa Naftzger, Sudhir Jaiswal and Keith Wycoff, *Production of secretory IgA antibodies in plants [Review]* 18 BIOMOLECULAR ENGINEERING 87-94 (2001).

[64]For a description of the state of the industry, and an assessment of biopharming's potential, *see*, C.L. Cramer, J. G. Booth, K. K. Oishi, *Transgenic Plants for Therapeutic Proteins:Linking Upstream and Downstream Strategies*, in CURRENT TOPICS IN MICROBIOLOGY & IMMUNOLOGY 95-118 (1999)(exploring the advantages of plant-based production of biologics).

The range of possible biopharm products under development is truly staggering.[65] For example, researchers at the Washington State University have transformed barley so that it produces α_1-antitrypsin–a human blood plasma protein used to treat cystic fibrosis and various skin diseases.[66] Barley has also been transformed to produce Antithrombin III-a human anticoagualant.[67] There has been a great deal of research on antibody production in biopharm plants–so called "plantibodies"[68] and various research teams have demonstrated the possibilities of growing biovaccines against infectious diseases like cholera,[69] hepatitis B,[70] Norwalk virus[71] and traveler's diarrhea.[72] Pre-clinical trials for these biovaccines have demonstrated that plant-

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[65]A partial list of these products is available in Cramer, *Transgenic plants for Therapeutic Proteins*, at 97, supra n. _.

[66]See, H. Horvath , J. Huang, O.T. Wong, E. Kohl, T. Okita, C.G. Kannangara & D.von Wettstein, *The production of recombinant proteins in transgenic barley grains*, 97 PROC. NATL. ACAD. SCI. 1914-1919 (2000). For a detailed description of the transformation, see Professor Diter von Wettstein, Application for Permit #00-334-01R Renewal under 7 CFR 340 (April 30, 2002). Currently this protein is available in limited supply form human blood plasma. If biopharming successfully increases the supply, α_1-antitrypsin could be used to treat a wide range of disorders more effectively. Id. at 5.

[67]Von Wettstein, Permit Renewal at 5, supra n. __.

[68]Daniell, *Medical Molecular Farming*, 6 TRENDS IN PLANT SCI. at 221, fig. 1 (describing current human and mammalian trials of these plantibodies).

[69]Takeshi Arakawa, et al, *Expression of cholera toxin B subunit oligomers in transgenic potato plants*, 6 TRANSGENIC RESEARCH 403-413 (1997).

[70]J. Kapusta, et al., *A plant-derived edible vaccine against Hepatitis B*, 13 FASEB Journal 1796 (Oct. 1999)

[71]Carol O. Tacket, et al, *Human Immune Responses to a Novel Norwalk Virus Vaccine Delivered in Transgenic Potatoes–Concise Communication*, 182 J. INFECT. DIS. 302-05 (July 2000).

[72]Carol O Tacket, et al., *Immunogenicity in humans of a recombinant bacterial antigen delivered in a transgenic potato*, 4 NATURE MEDICINE 607 (May 1998).

grown vaccines can be effective in humans.[73] Researchers at ProdiGene and Epicyte have transformed corn to produce human monoclonal antibodies to treat HIV,[74] and herpes simplex,[75] and a team at Cornell has developed individualized biovaccines to treat non-Hodgkin's lymphoma.[76] ProdiGene currently biopharms avidin corn for use as a research grade chemical,[77] and Epicyte has developed a corn-grown spermicidal plantibody that it hopes to market as a contraceptive.[78]

Although biopharm research has been conducted on a wide variety of plant species, corn has become the crop of choice for biopharm companies looking to commercialize their products.[79]

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[73]Carol O. Tacket, et al, *Immunogenicity in Humans of a Recombinant Bacterial Antigen Delivered in a Transgenic Potato,* 4 NATURE MEDICINE 607 (May 1998); J. Kapusta, et al., *A plant-derived edible vaccine against Hepatitis B*, 13 FASEB Journal 1796 (Oct. 1999); for discussion of another experiment with a biovaccine, see, A Modelska, et al, *Immunization against rabies with plant derived antigin,* 95 Proc. Natl. Acad. Sci. USA 2481(1998).

[74]*See*, Press Release, *Epicyte Pharmaceutical Advances Production of Human HIV Antibodies in Plants,* available at: http://www.epicyte.com/general/content/pressRoom/press_releases/01-28-03.pdf.

[75]Larry Zeitlin, Stuart S. Olmsted, Thomas R. Moench, Man Sung Co, Brian J. Martinell, Vikram M. Paradkar, David R. Russell, Cary Queen, Richard A. Cone, Kevin J. Whaley, *A humanized monoclonal antibody produced in transgenic plants for immunoprotection of the vagina against genital herpes*, 16 NATURE BIOTECHNOLOGY 1361 (Dec. 1998), available at http://www.epicyte.com/general/content/pressRoom/papers/12-98.pdf.

[76]Alison A. McCormick, et al, *Rapid production of specific vaccines for lymphoma by expression of the tumor-derived single-chain Fv epitopes in tobacco plants*, 96 Proc. Natl. Acad. Sci. 703-708 (Jan. 1999).

[77]Elizabeth E. Hood, et al, *Commercial Production of avidin from transgenic maize: characterization of transformant, production, processing, extraction and purification*, 3 MOLECULAR BREEDING 291-306 (1997).

[78]See, Cone, et al, Topical Application of Antibodies for Contraception and for Prophylaxis Against Sexually Transmitted Diseases, US Patent No. 6,355,235, (Mar. 12, 2002), (describing the antibodies as extremely effective in small doses) available at http://www.epicyte.com/technology/patents/US6,355,235.pdf.

[79]MANUFACTURING DRUGS, at 41 (reporting that 134 of USDA's 198 biopharm field trial notifications or permits were for corn).

Indeed, the number of corn field tests dwarfs experimentation in all other crops combined.[80] Corn does offer a number of advantages–particularly the utility of corn cobs as a pre-packaged, cheap and easily transported storage system. Unfortunately, this use of corn raises some serious safety questions because of the likelihood of contaminating the food supply. Corn is, after all, a promiscuously outcrossing, wind-pollinated plant. Although companies routinely claim that test site locations are confidential business information,[81] rendering that information unavailable to the public, much of this testing apparently occurred in the corn belt.

B. United States Policy Towards Biopharming

Biopharming is an integral part of President Bush's energy policy and associated initiatives and was strongly supported by President Clinton before him. In 2000, Congress passed the Biomass Research and Development Act,[82] which created an interagency Biomass Research and Development Board and a Biomass Research and Development Technical Advisory Committee.[83] In 2002, the Advisory Committee published a National Vision Statement and a Biomass Roadmap for bioenergy and biobased products.[84] The Vision Statement sets a goal of satisfying 18% of the 2010 production target of chemical commodities through biobased production.[85] One of the

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[80]Id.

[81]ENVIRONMENTAL EFFECTS, at 11, supra n. __ (noting that the extent of CBI claimed by registrants hampers external review and transparency of the decisionmaking process).

[82]Biomass Research and Development Act, Title III of the Agricultural Risk Protection Act, P.L. 106-224 (June 2000).

[83]Id.

[84]See, Vision for Bioenergy & Biobased Prodcuts in the United States (Oct. 2002)(hereafter Vision Statement); Roadmap for Biomass Technologies in the United States, (Dec. 2002)(hereafter Biomass Roadmap). Both of these documents are available at: http://www.oit.doe.gov/agriculture/.

[85]Vision Statement at ___.

articulated, and oft repeated goals of the Vision Statement and its accompanying Roadmap was "remov[al of] the barriers facing biomass technologies."[86] The Committee's charge extends to all biobased industries, including biopharming.

Although this Committee was a joint project between the Departments of Energy and Agriculture, the Vision Statement and Biomass Roadmap were emphatically a product of the interested industries. Indeed, USDA unambiguously described the Vision Statement and the Biomass Roadmap as articulating the industries' vision for their future.[87] Perhaps not surprisingly, the tenor of the Committee's public policy recommendations was to support and facilitate development of biobased industry and to downplay any drawbacks.[88] Nowhere in these recommendations is any discussion of the very serious public health[89] and environmental[90] concerns posed by this new technology.

In shelving these concerns in favor of promoting industrial "progress", the Committee was merely continuing a tradition that had earlier been established by the Department of Energy. In 1998, the Department of Energy's Office of Industrial Technology (OIT) sponsored the Agricultural Industries of the Future (OIF) as a public/private collaboration to plan the future of

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[86]Vision Statement, at 3, 9, 11; Biomass Roadmap at ___.

[87]Industries of the Future, available at http://www.oit.doe.gov/agriculture/#left.

[88]Biomass Roadmap, p. 27.

[89]The potential for these non-food proteins to render otherwise unidentifiable foods either allergenic or toxic to consumers is the most prominent of these public health concerns. Because biopharm crops look exactly like conventional crops, a consumer will have no way to know if she is inadvertantly consuming dangerous compounds.

[90]For example, the National Research Council has suggested that large-scale biobased production would necessitate withdrawing half the land currently fallow under the Conservation Reserve Program. BIOBASED INDUSTRIAL PRODUCTS: PRIORITIES FOR RESEARCH AND COMMERCIALIZATION (2000) at p. 4.

industrial biopharming.[91] This group produced two critical documents: The Vision for Bioenergy and Biobased Products in the United States,[92] and the Technology Roadmap for Plant/Crop-Based Renewable Resources 2020.[93] The Technology Roadmap set a target that, by 2020, 10% of all chemical feedstock demand be satisfied through biopharming.[94] The DOE made it clear that the Technology Roadmap was "driven by industry" and that OIT's role was to "support the development and deployment of technologies that will shape the future of the agriculture industry."[95]

The Technology Roadmap was intended to "encourage industry to undertake long-term, sector-wide technology planning."[96] Conspicuously absent from this long-term, sector-wide planning is any consideration of the serious threats that improperly managed biopharm crops will pose to the United States' food supply. Protecting the integrity of the food supply is not among the priorities identified in the Roadmap, and environmental protection is thrown in as an

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[91]Office of Industrial Technology, Agriculture Compact, available at: http://www.oit.doe.gov/agriculture/compact.shtml.

[92]Vision for Bioenergy and Biobased Products in the United States, available at: http://www.bioproducts-bioenergy.gov/pdfs/BioVision_03_Web.pdf.

[93]Technology Roadmap for PlantCrop-Based Renewable Resources 2020, p. 10, DOE/GO 10099-706 (Feb. 1999), available at: www.oit.doe.gov/agriculture/ (hereafter "Technology Roadmap").

[94]Id, at 10. Despite being available from the DOE website and various other indicia of government sanction (including participation of DOE and USDA officials), DOE describes the Technology Roadmap as a process initiated by the National Corn Growers Association, and produced by organizations representing the U.S. agricultural, forestry, and chemical companies. Office of Industrial Technologies, *Visions and Roadmaps*, available at http://www.oit.doe.gov/agriculture/visions.shtml.

[95]Id.

[96]Id.

afterthought.[97] No consumer or environmental NGOs, no public health experts, and for that matter no FDA or EPA officials participated in the workshops that produced the Roadmap.[98] The only USDA officials were from the Agricultural Research Service (ARS),[99] USDA's in-house biopharm research arm. No APHIS officials experienced in the logistical problems of trying to prevent cross-contamination and commingling of agricultural crops were invited to participate.

It was a serious mistake to exclude these important stakeholders from the "long-term sector-wide" planning process. The Vison Statements and Roadmaps produced under these circumstances were seriously flawed and are unable to cope with the very real problems posed by biopharming.

II. Regulatory Gaps and Biopharming

USDA has little experience or familiarity with the non-food compounds involved in biopharming,[100] some of which are known to have deleterious effects on human health. For example, the first commercialized biopharm crop is a corn plant engineered to produce industrial grade avidin, a diagnostic reagent isolated from chicken egg.[101] Avidin is known to cause Vitamin

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[97]Technology Roadmap, p. 10.

[98]Id, Appendix 5.

[99]The Agricultural Research Service (ARS) is the in-house research agency of the U.S. Department of Agriculture. ARS conducts extensive biopharm research focusing on "developing feedstocks and industrial products, including biofuels and bioenergy, that expand markets for agricultural materials, replace imports and petroleum-based products, and offer opportunity to meet environmental needs. This includes developing, modifying and utilizing new and advanced technologies to convert plant and animal commodities and by-products to new products and by developing energy crops as well as new crops to meet niche market opportunities." This description of ARS is available at: BBCC Member Agencies, http://www.ars.usda.gov/Bbcc/USDA_BBCC.htm. Given ARS's mandate, it is difficult to imagine the agency as a voice for caution in the Roadmap process.

[100] Interim Rule Fed. Reg. 46,434, supra n. __.

[101]Elizabeth E. Hood, et al, *Commercial Production of avidin from transgenic maize: characterization of transformant, production, processing, extraction and purification*, 3 MOLECULAR BREEDING 291-306 (1997).

B deficiency upon excessive ingestion.[102] The National Academy of Science has been extremely critical of USDA's handling of avidin corn, calling it an example of lax and inadequate regulation.[103] Other biopharm crops similarly produce compounds not intended for consumption as food–indeed many are intended for oral delivery of medicines.

There has been little assessment of the potential health impacts from food contaminated with these or any other biopharm crops. Despite a clear likelihood that people will be ingesting these antibodies, plastics, and vaccines with their cornflakes, we have no knowledge about the health effects of consuming these compounds. Exposure through ingestion raises serious questions that should be answered before these crops are commercialized and grown in uncontrolled conditions. Unfortunately, this means of exposure falls entirely outside the existing regulatory scheme and is completely unregulated. Because the crops are not intended for food, they fall entirely outside FDA's regulatory authority (although the drugs produced through biopharming will be regulated in accordance with existing regulations designed to ensure safety and efficacy). Nor does USDA evaluate the health effects of contamination in its permit process. Instead, USDA imposes a series of physical containment measures on these crops and then assumes that these measures will prevent contamination of the food supply. This reliance on physical containment measures flies in the face of all available information about how such measures actually work.

A. Past as Prologue: The Biotech Industry's Unsuccessful Past Attempts at Physical Containment

Although few biopharm crops have been commercialized, the first generation of GM crops have been planted commercially for the past six years–enough time to develop some sense of how well required physical containment measures are being implemented for those crops. Unfortunately, industry's track record on successfully containing GM crops is singularly

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[102]MANUFACTURING DRUGS at Appendix 2.

[103]Environmental Effects, at 180-82, supra n. __.

unimpressive. A series of near miss disasters has undermined public confidence in existing regulatory processes.

StarLink corn is by far the most famous example of how poorly physical containment measures prevent contamination of the food supply when a food crop is genetically modified in a manner that precludes its use as food.[104] StarLink corn was genetically engineered to produce Bt toxin[105] –a pesticide toxic to some common lepidopteran pests.[106] Because of the particular nature of the genetic transformation involved in creating StarLink corn,[107] there were unanswered questions about whether StarLink corn was a human allergen.[108] As a result of these allergenicity concerns, StarLink corn was not approved for use as human food.[109] In order to get permission

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[104]See, Rebecca Bratspies, Myths of Voluntary Compliance: Lessons from the StarLink Corn Fiasco, 27 Wm. & Mary Envtl. L. & Pol'y Rev. 593 (2003); Mandel, *Gaps, Inexperiences and Inconsistencies*, supra n. ___.

[105]StarLink corn was genetically engineered to contain two novel genes—one conveying herbicide tolerance and one conveying insect resistance. USDA/APHIS Petition 97-265-01p for Determination of Non-Regulated Status for Bt Cry9C Insect Resistant and Glufosinate Tolerant Corn Transformation Event CBH-351, May 1998, at 6-9 [hereinafter StarLink Non-Regulated Determination], *available at* http://www.aphis.usda.gov/biotech/dec_docs/9726501p_ea.HTM. The herbicide tolerance gene was the product of an earlier approval process. It was the addition of a gene derived from the bacterial species Bacillus thuringiensis (Bt), coding for an insecticidal protein called Cry9C, that triggered the StarLink crisis.

[106]Lepidoptera is a large order of insects, comprised of butterflies and moths. For a description of the biological mechanism by which Bt kills Lepidopteran pests, see INT'L LIFE SCI. INST., AN EVALUATION OF INSECT RESISTANCE MANAGEMENT IN BT FIELD CORN: A SCIENCE BASED FRAMEWORK FOR RISK ASSESSMENT AND RISK MANAGEMENT 9-10 (1998).

[107]Cry9C, the Bt protein incorporated into StarLink corn shared properties with some known food allergens. *See* Report, ENVIRONMENTAL HEALTH DIVISION, CENTER FOR DISEASE CONTROL, INVESTIGATION OF HUMAN HEALTH EFFECTS ASSOCIATED WITH POTENTIAL EXPOSURE TO GENETICALLY MODIFIED CORN, (2001) [hereinafter CDC REPORT], *available at* http://www.cdc.gov/nceh/ehhe/Cry9cReport.

[108] Marc Kaufman, *Biotech Critics cite unapproved corn in taco shells; gene-modified variety allowed only for animal feed because of allergy concerns* Washington Post, September 18, 2000 p. A.2.

[109] Approval of Pesticide Product Registrations, 63 Fed. Reg. 28,258-61 (May 22, 1998); *see also* MIKE MENDELSOHN, EPA, PESTICIDE FACT SHEET: BT CRY9C IN CORN (Apr. 1, 2000) 5 *available upon request at* http://www.epa.gov/opprd001/factsheets/pmcontacts.htm.

to market StarLink corn for animal feed or industrial uses, its manufacturer assured government regulators that the corn would be kept out of the human food supply.[110]

In September of 2000, however, a coalition of environmental groups announced that they had discovered StarLink corn in 23 common grocery products.[111] The announcement set off a frenzy of product recalls and consumer panic.[112] Ultimately, the unapproved an possibly dangerous corn was discovered in more than 300 types of processed foods that had to be pulled from grocery shelves around the world.[113] Under heavy pressure from USDA, StarLink's manufacturer Aventis contacted growers and repurchased their remaining StarLink corn to ensure that no more of it entered the food supply. These efforts were relatively successful and most of the StarLink crop was removed from the food supply. Although there was a "medium likelihood" that StarLink corn was allergenic,[114] the anti-GM activists had caught the contamination before most of the non-food corn had entered the food supply. Therefore, CDC and FDA concluded that based on

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[110]Matt Crenson, *Rules for Genetically Modified Corn Broke Down Between Seed Plant, Farm*, ST. LOUIS POST-DISPATCH, Dec. 15, 2000, at A10.

[111]*StarLink Corn: How it Reached the Food Supply*, A.P., Dec. 4, 2002, *available at* http://archive.showmenews.com/2000/dec/ 20001204busi011.asp.

[112] *See, e.g., Biotech Corn Recall Expands in Stores, Restaurants*, WASH. POST, Nov. 3, 2000, at A5; *50% of Corn May be Impure; Problem Could Cost Hundreds of Millions*, DES MOINES REG., Oct. 28, 2000, at 1A; Mark Kaufman, *Corn Woes Prompt Kellogg Plant Shutdown*, WASH. POST, Oct. 21, 2000 at A2; *Western Family Recalls Products with Altered Corn*, THE OREGONIAN, Oct. 26, 2000, at A2, *available at* 2000 WL 27103380.

[113] FDA Enforcement Report for November 1, 2000, *available at* http://www.fda.gov/bbs/topics/ENFORCE/ ENF00666.html. Millions of bushels of StarLink corn had been commingled with food corn in at least 350 grain elevators. Kurt Eichenwald, *New Concerns Rise on Keeping Track of Modified Corn*, N.Y. TIMES, Oct. 14, 2000, at A1

[114] *See* CDC REPORT, *supra* note __. Blood tests failed to find signs of antibodies to the protein in the genetically engineered corn. Thus, the federal Centers for Disease Control and Prevention concluded that although the study participants may have experienced allergic reactions, based upon the results of their study alone, CDC "could not conclude that a reported illness was a [StarLink] allergic reaction." CDC also cautioned that they could not rule out the possibility because food allergies may occur without detectible serum antibodies to the antigen.

the low exposure there was only a "low probability" that consumers would actually develop allergies to it.[115]

Even so, the StarLink fiasco had a devastating effect on consumer confidence in biotechnology[116] and raised troubling questions about whether the integrity of the food supply is adequately protected. After all, it was only because GM opponents independently tested packaged corn foods for StarLink contamination and then gave their discovery of contamination so much publicity that so little StarLink corn made it into the food supply–that fortunate situation owed nothing to the effectiveness of regulatory oversight. The crisis also devastated United States grain exports.[117]

Another notorious incident involved two biopharm corn test plots planted by one of biopharming's leading companies, ProdiGene. ProdiGene was the first company to develop and commercialize a biopharmed product.[118] Among the advantages ProdiGene touts for its "plant delivery system" is a "comprehensive Compliance Plus System that demonstrates a strong commitment to proactive safety measures."[119] Twice in 2002, this "Compliance Plus System" failed to ensure that the most basic preventative measures were observed at two ProdiGene test sites.

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[115] CDC REPORT; *see also,* FIFRA SAP, ASSESSMENT OF SCIENTIFIC INFORMATION CONCERNING STARLINK™ CORN, SAP Report No. 2000-06 (2000), *available at* http://www.epa.gov/scipoly/sap/2000/ index.htm.

[116]The presence of StarLink corn in human food was unambiguously unlawful, rendering the foods in question adulterated under the Food, Drug and Cosmetic Act, and violating the corn's Plant Incorporated Pesticide Registration. *See* Bacillus Thuringiensis subspecies tolworthi Cry9C Protein and the Genetic Material Necessary for its Production in Corn: Exemption From the Requirement of a Tolerance, 63 Fed. Reg. 28,258 (May 22, 1998). This exemption regulation eliminated the need to establish a maximum permissible level for residues of this plant pesticide in, or on, corn used for feed, as well as in meat, poultry, milk or eggs resulting from animals fed such feed. The exemption specifically did not permit human consumption of the StarLink corn itself.

[117] For a full exploration of the StarLink crisis, *see* Bratspies, Myths of Voluntary Compliance, supra n. ___.

[118]ProdiGene, Plant Biotechnology Intro, available at http://www.prodigene.com/0201.htm.

[119]ProdiGene, Our Technology Platform, available at http://www.prodigene.com/0202.htm.

Indeed, recently disclosed APHIS records reveal that before these incidents, Prodigene had already racked up a lengthy series of violations over an extended period of time, with few if any consequences.[120]

ProdiGene's 2002 violations again involved failures to implement legally required physical containment measures. Both violations occurred in the corn belt–one in Nebraska and the other in Iowa.[121] At both sites, government inspectors discovered ProdiGene corn, which had been engineered to produce a swine vaccine, growing amidst soybeans destined for human consumption.[122] These plants were "volunteers" having grown from seeds left in the soil from a prior year's field trial. Despite a warning to destroy the biopharm corn,[123] the Nebraska grower instead harvested his fields and sent the soybeans to an elevator where stalks and leaves from the bioengineered corn were commingled with the soybeans already present in the elevator.[124] Because the soybeans were now contaminated with the non-food biopharm corn, APHIS ordered the destruction of all 500,000 bushels of soybeans in the elevator.[125] In response to the Iowa violations, APHIS ordered Prodigene to uproot and destroy 155 acres of surrounding conventional corn because the biopharm corn was not adequately separated and therefore might have pollinated

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[120]CITE APHIS STATS

[121] USDA Investigates Biotech Company for Possible Permit Violations (November 13, 2002) available at: http://aphisweb.aphis.usda.gov/lpa/news/2002/11/prodigene.html.

[122] *Agriculture Department Fines ProdiGene for Biotech Mishaps* (Dec. 7, 2002), *at* http://earthboundfarm.com/news-world/GMOfine.html; *Feds Probe Biotech Firm for Crop Mixing*, Nov. 12, 2002, *at* http://www.cnn.com /2002/US/11/14/biotech.contamination/.

[123]Philip Brasher, *Biotech Corn May Have Tainted Soybeans*, DES MOINES REG., Nov. 13, 2002, at 1A.

[124] *Id. See also, Corn Near Gene-Altered Site to be Destroyed*, N.Y. TIMES, Nov. 14, 2002, at C10

[125] *Id. (citing to both articles–can I do that??)*

the food corn.[126] USDA levied a $250,000 fine against Prodigene, but the underlying problem remains.[127] Clear and legally binding requirements for how this biopharm crop was to be handled were ignored.[128] The ProdiGene incidents illustrate the problems inherent to using food plants to produce non-food drugs or industrial feedstocks. Such drug-producing varieties are not fungible--that is, they are not interchangeable for varieties that produce food-grade corn. In this case, none of the biopharmed corn seems to have made it all the way into the food supply, but it was a close call.

Unfortunately, StarLink and ProdiGene are not the only examples of how lax compliance with physical segregation requirements threatens the United States' food supply. As 2002 drew to a close, EPA announced it had levied fines against two more biotechnology firms, this time in Hawaii, for failure to properly manage experimental, and, therefore, non-food GM crops.[129] Dow Agrosciences and Pioneer Hi-Bred were both fined for failure to take proper measures to prevent corn intended for human consumption from being contaminated with experimental, non-approved

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[126] *Id. See also* Brasher, *supra* note ___; APHIS, USDA Investigates Biotech Company for Possible Permit Violations, available at: http://www.aphis.usda.gov/lpa/press/2002/11/prodigene.html.

[127] Press Release, Matt Lloyd & Jerry Redding, USDA Announces Actions Regarding Plant Protection Act Violations Involving ProdiGene Inc. (Dec. 6, 2002), *available at:* http://www.usda.gov/news/releases/2002/12/0498.htm. ProdiGene was assessed a $250,000 fine, and required to pay more than $3 million to repurchase the soybeans and to clean the silo. *See* Christopher Doering, *ProdiGene to Spend Millions on Bio-Corn Tainting*, Sept. 12, 2002, *available at:* http://www.planetark.org/avantgo/dailynewsstory.cfm?newsid=18935. USDA also required Prodigene to post a $1 million bond, and to comply with additional compliance standards, including additional approvals before field testing and harvesting genetically modified material. The company will be required to develop a written compliance program designed to ensure future compliance with the Plant Protection Act, federal regulations and permit conditions. Lloyd & Redding, supra.

[128] Brasher, *supra* note ___.

[129] Justin Gillis, *EPA Fines Biotechs for Corn Violations*, WASH. POST, Dec. 13, 2002, at E3; Justin Gillis, *Corn Growing Far Afield? A Mishap with Gene-altered Grain Spotlights the Odds of Contamination*, WASH. POST, Nov. 16, 2002. Because the experimental GM corn involved in these incidents was engineered to produce a pesticide, the field test fell under EPA's FIFRA authority.

GM corn.[130] As part of the settlements, both companies reaffirmed their commitment to following permit conditions in the future and to immediately reporting any irregularities or violations.[131] Just four months later, however, Pioneer was again in hot water. EPA fined the company $72,000 for failing to notify EPA immediately of a new incident in which experimental, non-food corn contaminated food crops.[132]

These incidents are only the most public face of a growing problem of contamination and commingling. In October of 2003, APHIS revealed for the first time that Monsanto and its partners violated federal regulations for planting biopharmed or otherwise unapproved GM crops 44 times from 1990 to 2001 and paid $69,550 in fines in four of those cases.[133] In 2003, Monsanto also discovered that its Roundup Ready "Quest" canola seeds were contaminated with an unapproved transgene, necessitating the urgent recall of thousands of bags of canola seed during planting season.[134]

The growing evidence of cross contamination from biopharm and experimental GM crops raises serious questions about the overall likelihood that biopharming can be done safely in food

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[130] *Id.* On a related note, FDA is investigating whether genetically modified pigs were improperly sold into the human food supply. Aaron Zitner, *Pigs in Genetic Study May Have Ended Up as Food*, L.A. TIMES, Feb. 6, 2003, at 17. This incident underscores the very real possibilities that any GM products might wind up in the human food supply. The likely effects of a failure to segregate must be considered at the approval stage.

[131]Justin Gillis, *EPA Fines Biotechs for Corn Violations*, WASH. POST, Dec. 13, 2002, at E3. See also, Two Biotech Companies Fined for Violations, December 16, 2002, available at http://www.ens-news.com/ens/dec2002/2002-12-16-09.asp#anchor4.

[132]Randi Fabi, *Pioneer Biotech Corn Taints Hawaii Crop*, Reuters March 24, 2003; Justin Gillis, *Firm Fined for Spread Of Altered Corn Genes: Government Wasn't Told Soon Enough*, WASH. POST at E.4.

[133]CITE.

[134]Judy Steed, *Seeds of Conflict* Toronto Star, November 10, 2003. This discovery was reminiscent of Garth seed's discovery in 2000 that StarLink transgenes had contaminated other hybrid corn varieties. CITE>

crops.[135] This history of multiple lapses and failures to follow containment protocols do not bode well for safe use of this technology. That basic safety precautions were not taken during the earliest stages of the technology's development ought to raise alarms about what will happen if the crops ever go into full-scale production. Environmental and human health impacts of biopharming will only increase as more and more of these crops are planted. These concerns are magnified by proposals to produce more than one novel protein simultaneously in the same plant, and/or to reuse the crops as food once the biopharm compounds have been extracted, a proposal known as "co-production."[136]

B. USDA Has Abdicated Its Regulatory Responsibilities

The United States has no comprehensive statute addressing the testing and monitoring of genetically altered products. Indeed, such products have never been tested for long-term effects on human health. Rather, genetically altered products are regulated under existing statutes relating to food, drugs, agriculture, or the environment based on the product's intended use.[137] FDA,[138]

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[135]ADD EU, GREENPEACE AND CANADA STUFF

[136]BIOBASED INDUSTRIAL PRODUCTS p. 4 (emphasizing that such "co-production" could minimize conflicts with use of land for food production); Giddings, et. al, *Transgenic Plants as factories for biopharmaceuticals*, 18 Nature Biotechnology 1151(2000) (suggesting that the costs of purifying specialty chemicals could be defrayed by selling the food components of the crop).

[137]See, Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302 (June 26, 1986).

[138]FDA regulates biotechnology products under statutes relating to food (except for meat, poultry, and egg products, which are regulated by the USDA), feed, drugs, and medical devices. See Federal Food, Drug and Cosmetic Act (FFDCA), 21 U.S.C. §§ 301, 395 (1994); 21 C.F.R. §§ 171.1-571.1 (2000). In May 1992, the FDA published a policy statement regarding food derived from new plant varieties. In this statement, the FDA concluded that food and feed derived from genetically modified organisms should be regulated in the same manner as food and feed derived from traditionally bred plants, which leaves the responsibility of assuring the safety of the food with the producer. See, Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. 22,984 (May 29, 1992).

USDA,[139] and EPA[140] all have partial authority over various aspects of GM crops. In theory, under the Framework, USDA determines whether a GM crop is safe to grow, FDA if it is safe to seat, and EPA if it is safe for the environment.[141]

Biopharming does not fit well into this regulatory scheme. Although the therapeutics produced through biopharming will be drugs (and will thus be subject to FDA's traditional drug safety evaluations under the FFDCA), the crops themselves are neither drugs nor food. Thus, even though it is inevitable that these biopharm products will find their way into the food supply, the biopharm crops fall entirely outside FDA's scope of authority. Unless the biopharm crops also produce pesticides, EPA has no authority over these crops either–even though there are clear environmental risks from spread of biopharm pollens or proteins. Thus, it falls solely to USDA to regulate biopharming.

Under the best of circumstances, properly regulating these crops would be a daunting task. Circumstances are, however, far from ideal. USDA regulates these crops under the same authority it uses to regulate other GM crops–the Plant Protection Act. The PPA focuses primarily on

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[139] USDA regulates biotech crops under the Plant Protection Act (PPA), 7 USC 7701-7772 (2000), which consolidated several previous statutes that APHIS used to regulate genetically engineered organisms, including the Federal Plant Pest Act, 7 USC 150aa-150jj, and the Plant Quarantine Act , 7 USC 151-164a, 166-167. The Secretary of Agriculture has delegated her authority under the PPA to APHIS, and I will use APHIS and USDA interchangeably in this discussion. Because no new regulations have yet been issued pursuant to the PPA, APHIS continues to regulate biotechnology products according to the regulations issued under the old statutes. For the USDA's Internet site on biotechnology, see http://www.aphis.usda.gov/biotech.

[140] EPA regulates genetically modified organisms primarily under statutes relating to toxic substances and pesticides. See Toxic Substances Control Act (TSCA), 15 U.S.C. §§ 2601-2629 (1994) (regulating toxic substances); Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), 7 U.S.C. §§ 136-136y (1994) (amended 1999) (regulating pesticides). Under TSCA, EPA regulates GM microorganisms, and under FIFRA it regulates so-called plant incorporated protectorants (like Bt crops) and pesticidal microorganisms. EPA also has responsibilities under the FFDCA, 21 U.S.C. § 346a(a)- (o) (1994) (regulating tolerances or exemptions for the requirement of a tolerance for pesticide residues in foods). Relevant regulations may be found at 40 C.F.R. § 152.1-.500, 2172.1-.59, 180.1-.1206, & 725.1 .1000 (2000).

[141]USDA, APHIS United States Regulatory Oversight in Biotechnology, available at www.aphis.usda.gov/biotech/OECD/usregs.htm#usdalaw.

agronomic risks, and does not give USDA a clear mandate to consider food safety or environmental concerns. Not only is its regulatory authority constrained, but USDA has an added problem–it holds conflicting mandates both to protect safety and to promote this new industry.

In 2002, Secretary Veneman established the Biobased Products and Bioenergy Coordination Council (BBCC)[142] to "facilitate and promote research, development, transfer of technology, commercialization, and marketing for biobased products and Bioenergy using renewable domestic agricultural (plant, animal, marine) and forestry materials."[143] Among the identified goals of the BBCC is "establish[ing] USDA as the lead advocate for the development and commercialization of biobased industrial and commercial products."[144] USDA, the lead regulatory agency, self-described itself as the technology's lead advocate and announced that it would " cooperate with the private sector in developing and demonstrating the potential commercial viability"[145] of biopharming. With the agency avowing an intent to encourage accelerated research anddevelopment,[146] who, if anyone, is protecting the public's interests in having this technology exploited only under conditions that protect human health and environmental safety?

This conflict between protection and promotion is visible in the regulatory scheme APHIS adopted. Until recently, scrutiny of biopharm crops was extremely light. Field tests could proceed under a streamlined notification process and no permit was required. On March 6, 2003, in

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[142] The Biobased Products and Bioenergy Coordination Council was established in 2002 by an order of Agriculture Secretary Ann M. Veneman. The Departmental regulation creating the BBCC is available at http://www.ars.usda.gov/Bbcc/DR9600-002.htm .

[143]Id.

[144]USDA, Strategic Plan for Biobased Products Through the Biobased Products and Bioenergy Coordination Council, available at http://www.ars.usda.gov/Bbcc/BBCC_strateg.htm.

[145]Id.

[146]Id.

response to the StarLink, ProdiGene, and Hawaii incidents, APHIS announced new requirements for biopharm crops to be implemented for the 2003 growing season and beyond.[147] In its summary of the new rules, APHIS emphasized that these biopharm products are never meant to enter the food supply and indicated that a stringent regulatory system would be necessary.[148] To that end, APHIS imposed safety measures based on plans for physical segregation. Seeking to control the likely routes for contamination, the new requirements introduced regular inspections, and imposed growing conditions and farm equipment standards. For the first time, there were: 1) mandatory field site inspections;[149] 2) a requirement that no biopharm corn be grown within one mile of open-pollinated corn;[150] and 3) restrictions on the production of food and feed crops at the field test site and perimeter fallow zone in the subsequent growing season.[151] In addition to these in-field physical containment measures, APHIS also imposed a series of logistical requirements designed to minimize contact. APHIS required that biopharm crops be planted and harvested with dedicated mechanized equipment that will be stored in dedicated facilities.[152] In addition, APHIS

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[147]Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11,337 (March 10, 2003).

[148]APHIS, Highlights of the Federal Register Notice, available at: http://www.usda.gov/news/releases/2003/03/aphisfactsheet030603.pdf.

[149] Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11,337 (March 10, 2003). Under the new regulations, every test site will be inspected during critical times in the biopharm production cycle. Up to five site visits might be made during the growing season, with another two for assessing volunteer plants the following year. Under the old rules, plots were rarely inspected.

[150] *Id.*11,338.

[151]*Id.*

[152]*Id.*

must approve equipment cleaning procedures,[153] and seed cleaning and drying procedures,[154] and all biopharm producers must attend a training program to increase the likelihood of compliance with permit conditions.[155]

APHIS characterized these new regulations as a revision of the regulatory framework "that reflects the latest science and information so that we can maintain the integrity of our systems."[156] Although APHIS claimed that the new conditions were "science based and reflect[ed] the anticipated increase of requests for permits for plants genetically engineered to produce pharmaceutical and industrial compounds,"[157] it is clear that this agency action was reactive rather than proactive. For example, until the 2003 growing season there were still no analogous (or for that matter any) requirements for industrial biopharm crop permits. On August 6, 2003, a full decade after the first field tests of industrial biopharm crops,[158] APHIS finally published an interim rule requiring that industrial biopharm crops be field tested, moved or imported only with a duly issued permit.[159] The interim rule will be in effect until December 2004.[160] Prior to 2003, field

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[153]*Id.*

[154]*Id.*

[155]*Id.*

[156]APHIS Press Release, USDA Strengthens 2003 Permit Conditions for Field Testing Genetically Engineered Plants, available at: http://www.usda.gov/news/releases/2003/03/aphis030603.htm (statement of Bobby Acord, APHIS Administrator).

[157]Id.

[158]Introduction of Plants Genetically Engineered to Produce Industrial Compounds, 68 Fed. Reg. 46434 (Aug. 6, 2003).

[159]*Id.*

[160]Id.

testing could be conducted under the expedited notification provisions–with no set standards for containment or oversight.[161] Between 1993 and 2001, APHIS received 10 notifications of introduction of plant-made industrials.[162] In the first half of 2003 alone, APHIS received 5 permit applications.[163] Only public disclosure of the ProdiGene near miss, coming on the heels of the StarLink fiasco prompted APHIS to act.

It remains to be seen how APHIS will administer its physical containment measures. As the crops move into commercial production, it is extremely unlikely that APHIS will be able to oversee or enforce these regulations. APHIS reports that in 2002, 130 acres of pharmaceutical biopharm crops were planted at 34 sites, most of which were smaller than 5 acres.[164] Thus, using 2002 as an example, APHIS new regulations would have required a minimum of 238 site visits (seven per site–five during the growing season and two thereafter). That number does not include any industrial sites. In 2000 and 2001, APHIS had 10 staff members to evaluate biotech applications.[165] Even before APHIS adopted this stepped up inspection regime, the National Research Council had concluded that APHIS did not have enough personnel to visit all the field test

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[161]Id.

[162]Id.at 46,435.

[163]Id. In March of 2003, APHIS published proposed rules for field testing plant-made pharmaceuticals and industrial chemicals. Proposed Rule, Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds , 68 Fed. Reg. 11337 (March 10, 2003). These proposed rules indicated that APHIS was considering extending permit requirements to plant-made industrials. In a press release that accompanied publication of the proposed rules, APHIS indicated that the agency intended to publish an interim final rule that will require a permit for the field testing of industrials for the 2003 growing season, and strongly encouraged any 2003 applicants to request a permit for field testing industrials. Accordingly, those entities submitting proposals in 2003 submitted permit applications rather than notifications.

[164]APHIS, Proposed Rules: Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11337, 11338 (Mar. 10 2003).

[165]Id. at p. 182.

sites and that many of the inspectors were poorly trained.[166] In years when there is an emergency priority, such as the recent European foot and mouth disease outbreak, there are even fewer inspectors available to inspect biopharm field tests.[167]

While APHIS might theoretically have the staff and resources to conduct 238 visits to the existing field trials, (the National Research Council concluded that there were 10 APHIS employees whose duties included inspecting these fields)[168] The agency has indicated that it expects requests for field test permits, and the scale of production to increase significantly over the next few years.[169] APHIS's overloaded staff already reviews approximately 1000 applications for field testing and deregulation of transgenic plants each year.[170] It is hard to imagine agency resources stretching farther. Certainly if the United States achieves the Roadmap vision of biopharming producing 10% of chemical feedstocks by 2020 (and that figure does not include the expected boom in biopharmaceuticals!!) APHIS will clearly not be able to conduct all the required visits. Indeed, the number of test plantings will not have to increase by much before APHIS's resources will be inadequate to make the promised seven visits over two years to each test plot. Moreover, once full production begins, there is no way the agency could visit every commercial grower on such a schedule.

Without this critical piece of the regulatory patchwork, it is unclear how APHIS envisions

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[166]Id.

[167]Id.

[168]National Research Council, ENVIRONMENTAL EFFECTS OF TRANSGENIC PLANTS: THE SCOPE AND ADEQUACY OF REGULATION, (2002) p. ___.

[169]Id.

[170]National Research Council, ENVIRONMENTAL EFFECTS OF TRANSGENIC PLANTS: THE SCOPE AND ADEQUACY OF REGULATION, (2002) p. 1.

fulfilling its compliance monitoring obligations, particularly since GM purveyors routinely use CBI claims to keep field test locations secret. Coupled with the lack of oversight staff, this prevalence of CBI claims is particularly troubling. While the companies have a legitimate interest in preventing corporate vandalism or corporate espionage, the public has a strong interest in knowing whether biopharmed crops are contaminating adjacent conventional crops with substances that are clearly not intended for human or animal consumption. Secrecy eliminates the possibility that private actors will be able to independently monitor contamination levels. Since there is no governmental monitoring system, and no requirement that the GM purveyors monitor surrounding fields for contamination, shutting off the possibility of third-party monitoring means that there will be no monitoring of any kind. Since the StarLink fiasco came to light solely as a result of vigilant third-party monitoring, this lack is particularly ill-adapted to creating a responsible and trustworthy regulatory scheme.

Indeed, because of these exact same constraints, physical containment measures have achieved only marginal success as a risk management tool for other GM crops, in particular those crops modified to express Bt toxins. Because of concerns about rapid evolution of pest resistance, EPA has developed some simple conditions for how Bt crops can be planted. In particular, EPA requires that at most 80% of the corn on a farm be Bt corn, with the other 20% conventional corn.[171] In addition, these conventional corn refuges must be planted within 1/4 mile of the Bt fields. An industry survey conducted during the 2002 growing season indicated that 11% of farmers failed to comply with these requirements.[172] The Center for Science in the Public Interest examined a parallel set of data submitted to USDA's National Agricultural Statistical Service (NASS), and discovered that growers self-reported information that amounted to non-compliance

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[171]See, *Biopesticides Registration Action Document:* Bacillus thuringiensis (Bt) *Plant-Incorporated Protectants,* at II.B.5 (Oct. 15, 2001), *available at* http://www.epa.gov/ pesticides/biopesticides/otherdocs/bt_brad2.

[172]Agricultural Biotechnology Stewardship Technical Committee, Insect Resistance Management Grower Survey for 2002 Bt Field Corn Growing Season, at http://www.ncga.com/biotechnology/pdfs/IRM_exec_summary.pdf.

levels 40% higher than those reported through the industry survey.[173] Similarly, a USDA review of compliance found that 20% of Bt corn growers failed to comply with federal growing requirements.[174] Prodigene certainly suggests that there is no reason to expect that biopharm growers will be any more compliant than are farmers growing other GM crops, and thus, depending on farmers to implement physical containment measures should not be the primary plan for keeping biopharm crops out of the food supply.

Even putting aside the careless or intentional acts at the root of StarLink (and Prodigene), the physical containment of living plants is next to impossible. Plants reseed themselves. It requires eternal vigilance on the part of the grower to eradicate any volunteer plants that grow the next season, and the volunteers might crop up either in nearby fields in addition to the test fields themselves. Such vigilance is both time consuming and expensive. The burdens these measures place on growers is a variable that is not easily captured by a regulatory system based on physical segregation. Because the risks are difficult to understand, and there is no way to recapture the added costs, growers are likely to slip up on their efforts. Any such lapses render physical containment measures–USDA's sole regulatory plan for protecting the food supply–wholly ineffective. These lapses are particularly likely because pollen drift is nearly impossible to control and is difficult to trace. This is a fatal flaw in USDA's decision to rely exclusively on physical containment measures, and it is not amenable to easy solution. For physical containment to have any hope of working, growers must be committed and dedicated to eradicating volunteers. Nevertheless, USDA requires no certification or special training for biopharmers, nor has USDA created a monitoring and reporting system to track the occurrence of volunteer plants. In fact,

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[173]Gregory Jaffe, Planting Trouble: Are Farmers Squandering Bt Corn Technology, Center for Science in the Public Interest, available at www.cspinet.org.

[174]Emily Gersema. *USDA Survey Shows Biotech Rules Breaches*, WASHINGTON POST (Sept. 10, 2003), available at: http://www.washingtonpost.com/ac2/wp-dyn/A57061-2003Sep10?language=printer.

USDA has no way to monitor either grower vigilance or actual incidents of contamination. Even if USDA required that growers report their planting patterns, and actually followed up to ensure that the plantings correctly matched the submitted patterns, such measures would bear no relationship to grower vigilance against volunteers and would utterly fail to detect contamination of nearby fields.

Compounding the problem, USDA has not required biopharm companies to develop tests to identify biopharm contamination, nor has it developed such tests on its own.[175] Remember, biopharm crops are phenotypically indistinguishable from food crops. Without a readily available and easily performed identity test, grain silos and food manufacturers have no way to know whether they are inadvertently purchasing biopharmed crops. We have seen this before. It was precisely this inability to distinguish food corn from non-food corn that gave rise to the StarLink fiasco. Successful risk management based on physical containment requires, at the very least, that contamination be readily identifiable.

In its most recent guidance to industry, USDA "strongly recommends," but does not require that companies develop tests to identify contamination in raw agricultural products.[176] A mere recommendation, however strong, is totally inappropriate here. Tests to discover contamination cannot be optional. In the absence of an express requirement, no biopharm developer has produced such a test. Without the test, there is no way to identify biopharm crops or contaminated crops and to ensure that such crops are diverted to nonfood uses. Moreover, UDSA's guidance does not suggest, "strongly" or otherwise, that biopharm purveyors monitor adjacent crops for evidence of contamination. Apparently, APHIS has satisfied itself that its proposed field practices will prevent contamination. APHIS inspectors will, at best, monitor to see

[175]Aventis had not developed any such tests for StarLink corn prior to the StarLink fiasco. One recommendation made in the aftermath of that incident was that the government ensure that such tests are developed prior to the release of a genetically engineered crop. See, Assessment of Additional Scientific Information Concerning StarLink Corn, FIFRA Scientific Advisory Panel, SAP Report No. 2002-09, p. 39.

[176]Guidance for Industry: Drugs Biologics and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals, available at: http://www.fda.gov/cber/gdlns/bioplant.htm.

if those field practices are being met. The agency has no intentions of monitoring, or requiring the biopharm purveyor to monitor, for actual contamination of nearby crops with non-food biopharm compounds. Thus there is no way to learn whether the physical containment practices that are APHIS's primary regulatory strategy are working or not. The National Research Council points to this "lack of rigor" in APHIS's procedures as a potential source of serious contamination problems.[177] Indeed, in other contexts, FDA recognizes "develop[ing], enhanc[ing], and maintain[ing] surveillance systems that can quickly and accurately identify food safety risks in the human food" as the key to an effective emergency response capability.[178] Because USDA does not require that tests be developed to identify contamination, there is no such surveillance system for biopharmed crops and no way to quickly respond to an emergency. In light of the industry's checkered history of contamination and commingling, there is no excuse for failing to require such tests.

III. Repairing the Inadequate and Porous Regulatory System

Non-food biotech products will enter the human food supply. After examining the prospect of corn biopharming in the corn belt, the National Research Council concluded that using food crops to produce non-edible and potentially harmful compounds creates serious regulatory issues.[179] In an unusually frank editorial, NATURE BIOTECHNOLOGY identified some of the major

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[177]Transgenic Plants p. 181. This NRC comment referred to field testing under notification. On August 6, 2003, APHIS issued an interim rule requiring that plants genetically modified to produce industrial compounds be field-tested only under a more rigorous permit system. APHIS, Introduction of plants Genetically Engineered to Produce Industrial Compounds, 68 Fed. Reg. 46,434 (August 6, 2003). For the 2003 growing season, APHIS had similarly decided that plants engineered to produce pharmaceutical compounds should be administered under permit rather than notification. See, 7 C.F.R. s340.3(b)(4)(iii). APHIS's identified rationale for this shift was its lack of regulatory experience or scientific familiarity with the non-food, non-feed nature of biopharming. 68 Fed. Reg. 46,434.

[178]Statement of Bernard A. Schwetz, D.V.M., Ph.D., Acting Principal Deputy Commissioner, Food and Drug Administration, BEFORE THE COMMITTEE ON GOVERNMENTAL AFFAIRS SUBCOMMITTEE ON OVERSIGHT OF GOVERNMENT MANAGEMENT, RESTRUCTURING and the DISTRICT OF COLUMBIA (October 10, 2001).

[179]ENVIRONMENTAL EFFECTS, at 229, supra n. __.

flaws with reliance on physical confinement–that gene-containment is next to impossible in the field and that farmers have proven to be unwilling or unable to follow planting rules.[180] USDA's regulatory scheme takes neither of these critical variables into account.

In the 1970's, scientists responded to growing concerns that biotechnology was developing more rapidly than was the ability to understand or manage the risks it posed by developing the Asilomar self-regulation plan. This plan was based on the conviction that standards of care should be "greater at the beginning and modified as improvements in the methodology occur and assessment of the risks change."[181] Those lessons have powerful resonance today in the context of biopharming. Much the same way the Asilomar Conference imposed a moratorium to permit the development of more information about risk, there should be a moratorium on field testing biopharm crops to permit information about risks to catch up to the biopharming industry's technical capabilities to convert plants into biofactories. If industry cannot, or will not, self-impose these sensible restrictions,[182] government must stand ready to take up the slack. Indeed, given the stakes, the government ought not be relying on industry self-regulation as its first line of defense. Instead, taking a leaf from the Asilomar Conference, APHIS should impose a temporary partial moratorium on biopharming. During this moratorium, which would be an interim period during which research on the health effects of these crops could be performed, the agency should restrict the technology to greenhouse plantings or to non-food crops. Such a decision would permit the technology to go forward, albeit more slowly, and with full respect for the many unknowns. Once more scientific information has been gathered, the agency and the public can make informed choices about the risks and benefits associated with biopharming.

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[180]Editorial, *Going with the Flow*, 20 NATURE BIOTECHNOLOGY 527 (June 2002).

[181]See, Berg, 188 SCIENCE at 992, supra n. __

[182]One critical difference between Asilomar and today is that most biopharm research is industry funded, and thus subject to commercial pressures from investors that Asilomar scientists did not have to face.

A. Possible FDA Regulatory Measures

A strong base of scientific knowledge is the foundation of any successful food safety system.[183] FDA claims that food safety must rest on strong "risk-based prevention standards to prevent contamination of all human foods and animal feeds over the farm-to-table continuum."[184] The risks here are plain and this same rigor must be brought to biopharm crops. Even in the face of USDA reluctance to involve FDA in approving biopharm crops, the agency need not be entirely passive. FDA could influence industry behavior by declaring "biopharm action levels"–the conditions under which the agency might seek to have a court find a food adulturated by biopharm crops.[185] By publically announcing its enforcement policy, FDA might spur industry to confront these questions and thus drive development of this technology towards safer options.[186] There is no justification for failing to use the full arsenal of agency powers to respond to this serious threat to the safety of the food supply.

Given what we know from experience with other GM crops, it is entirely inappropriate for the government to approach biopharming on a post hoc basis. Regulators must be involved at the planning stages–they cannot wait for developers come to the agencies with a largely completed product. At that point, modifications to protect public health are after the fact add ons–far more expensive and less effective than design modifications would have been during the development process.

B. Possible Biological Control Measures

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[183] National Academy of Sciences, ENSURING SAFE FOOD FROM PRODUCTION TO CONSUMPTION (August 1998)

[184] Id.

[185] 21 USCA §§ 331, 332, 342(a)(1) (2000); 20 CFR §§ 109.4, 109.6 (2000).

[186] See Daniel A. Farber, *Taking Slippage Seriously: Noncompliance and Creative Compliance in Environmental Law*, 23 Harv. Envtl. L. Rev. 297, 305- 09 (1999)(describing creative enforcement in the context of the Endangered Species Act.)

In the earliest stages of biotechnology, the Asilomar Conference recognized that "[t]he most significant contribution to limiting the spread of recombinant DNA is the use of biological barriers."[187] Somehow this initial insight was lost. Rather than a mere "additional factor of safety,"[188] physical containment measures have taken precedence as the primary means to contain biopharming's adverse effects. This inverted reliance on physical rather than biological containment measures must be reversed.

1. Use of Non-Food Crops

APHIS's post-Prodigene physical containment requirements mark a start towards responsible regulation. The requirements will undoubtedly strengthen the protections of the food supply, but they are too little, too late. There are other measures that would provide far greater protection, without simultaneously creating the need for a detailed and expensive oversight system.

The most obvious of these measures would be to require that biopharming be done only in non-food crops like tobacco, hemp or switch grass. Simply put, since it will not be possible to keep biopharm corn out of the food supply, food crops should not be productions vehicle for biopharming.[189] Such a rule would be the clearest way to protect public health while still permitting society to benefit from the potential represented by this new technology. In one fell swoop, USDA could eliminate any possibility of commingling. The clean regulatory line that "no biopharming in food crops" creates would also be easy to comply with–thus fitting neatly into the

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[187]Berg, 188 SCIENCE 992, supra n. __ .

[188]Id.

[189]In addition to contamination of the food supply, biopharming also raises questions about the environmental effects of gene flow to wild relatives. Twelve of the world's thirteen most important crops are known to hybridize with wild relatives somewhere in their agricultural range. Andow, *Consequences of Recurrent Gene Flow from Crops to Wild Relatives*, Proc. R.Soc. Lond. B. (April 14, 2003). Indeed, of the top sixty crop plants, only eleven do not hybridize with wild relatives somewhere in the world, and a majority have wild relatives in the United States. *Environmentally Friendly Approaches*, at 361, supra, n. __. These questions would not be resolved by restricting biopharming to non-food crops, though, because it would reduce the likelihood of contaminated pollen, chloroplast transformation would certainly reduce the environmental impacts these crops will have on natural ecosystems.

various vision statements and roadmaps aiming to nurture this technology by avoiding burdensome regulation. Moreover, many biopharm developers have hedged their bets and have proceeded with parallel development of biopharm crops in tobacco.[190] Thus, non-food biopharming could serve a dual public interest–providing access to needed therapeutics while, at the same time, weaning tobacco farmers from a perverse dependence on a continued market for cigarettes.

The biopharming industry itself agrees that it cannot afford another public relations disaster, and certainly not a public health catastrophe.[191] Food producers have called for a ban on biopharming in food crops.[192] The Grocery Manufacturers of America have urged biotech companies to stop using food crops as vehicles for growing biotech products that humans and animals are not supposed to eat.[193]

2. Chloroplast Transformation

At the very least, biopharm crops should always be modified through chloroplast transformation[194]–a means to produce high levels of novel proteins while ensuring that the pollen

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[190]See e.g., Margot Roosevelt, *Cures on the Cob*, TIME (May 26, 2003); see also Virginia Tech's Participatory Assessment of the Social and Economic Impacts of Biotechnology, available at http://www.agecon.vt.edu/biotechimpact/tobacco/WP20031.pdf.

[191]See, Justin Gillis, *Biotech Industry Adopts Precaution: Altered Plants Banned Near Major Food Crops*, WASH. POST, Oct. 22, 2002, at E1, available at: http://www.washingtonpost.com/wp-dyn/articles/A61908-2002Oct21.html (quoting Michael H. Pauley executive director of biotechnology for Epicyte Pharmaceutical Inc., which testing a herpes drug grown in corn as saying "I think we can all agree that this industry cannot afford StarLink II . . . .One incident like that is unacceptable. It's going to require a certain standard of behavior from the entire industry." *See also Careless Handling of Bioengineered Corn Causes Vast Repercussions in Industry,* ST. LOUIS DISPATCH, Nov. 22, 2002.

[192]Philip Brasher, *Biotech Firm Under Fire Has Links to Iowa*, Des Moines Register Nov. 14, 2002, available at http://desmoinesregister.com/business/stories/c4789013/19735220.html.

[193] Press Release, Grocery Manufacturers of America, GMA Urges the Use of Non-Food Crops for Biotech Drugs (Nov. 14, 2002), *at* http://www.gmabrands.com/news/docs/ NewsRelease.cfm?DocID=10298 (Nov. 14, 2002).

[194]Simon Geir Moller, Jodi Maple, Nam-Hai Chua, *The topological specificity factor AtMinE1 is essential for correct plastid division site placement in Arabidopsis*, __ The Plant Journal__ (2003).

does not contain transgenes.[195] Because chloroplasts are maternally inherited, there are usually no chloroplasts in pollen. Transforming chloroplast DNA rather than nuclear DNA would greatly reduce the threat of cross-pollination.[196] As such, this biological containment mechanism could be a partial solution to contamination of the food supply. Ideally those two biological safety measures should be combined so that biopharming occurs in non-food crops that have undergone chloroplast transformation. These biological segregation methods could be added to the physical segregation methods APHIS now imposes, but the need for oversight would be less pressing because the risks to human health would be radically reduced. Although biopharm crops have been developed enough to make these design modification choices expensive (and therefore unpalatable), it is not too late to require these sensible and practical restrictions on exploitation of the new technology.

3. Other Available Containment Measures

Making the biopharm crops "look different" would be another common sense precaution that would greatly reduce the risk to the food supply. More than a decade ago, researchers successfully engineered firefly luciferase[197] and green flourescent protein[198] into tobacco,

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[195]Henry Daniell, *GM crops: Public Perceptions and Scientific Solutions [Comment]*, 4 Trends in Plant Sci. 467, 468 (Dec. 1999); Henry Daniell, et al, *Containment of Herbicide Resistance Through Genetic Engineering of the Chloroplant Genome,* 16 Nat. Biotechnol. 345-48 (1998); S. Scott, M.J. Wilkinson, *Low Probability of Chloroplast Movement from Oil Rape (Brassica rapus) into Wild Brassical rapa,* 17 Nat. Biotechnol. 390-392 (1999).

[196]Some researchers believe that, because of their prokaryotic nature, chloroplasts are ideal for biopharming therapeutics that are currently produced in *E.coli* systems, including vaccines and antibodies. See, Darnell, Environmentally Friendly Approaches, 366, supra n. __.

[197] See, e.g., M. Schneider M, David Ow, S.H. Howell, *The in vivo pattern of firefly luciferase expression in transgenic plants,*14 Plant Mol Biol. 935-47 (1990): David Ow, et al., *Transient and stable expression of the firefly luciferase gene in plant cells and transgenic plants,* 234 Science 856-859 (1986).
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[198] Brian K. Harper, et al, *Green fluorescent protein as a marker for expression of a second gene in transgenic plants*, 17 Nature Biotech. 1125-1129 (1999); Staci Leffel, Stephen A. Mabon, and C. Neal Stewart, Jr, Tracking Transgenic Plants Using Green Flourescent Protein, available at http://www.isb.vt.edu/brarg/brasym96/leffel96.htm. The most famous use of this marker is the well-known photo of a "glow-in-the-dark" rabbit.

rendering the crop luminescent. Other phenotypic markers like restricting biopharming to purple maize varieties and banning the use of these varieties in food could also make tracking biopharm crops a more straightforward proposition and contamination more readily identifiable.

Another layer of protection could also be added through geographic containment–banning the planting of biopharm crops where their conventional counterparts are grown for food, and requiring extensive food safety testing before permitting field testing of any biopharm crop that is also used for food. Because this new technology will potentially be very lucrative,[199] such calls face stiff political opposition from cornbelt officials who do not want their states left out. Indeed, in the wake of the ProdiGene incident, a biotech industry trade group, BIO, issued a commitment not to grow biopharm corn in the cornbelt.[200] Reaction from cornbelt politicians was immediate and negative.[201] BIO quickly backed down. Only the federal government has the power to make such a rule stick, and the resources to provide enough of a countervailing benefit to make the rule palatable.

Any or all of these additional control measures would better protect the food supply than do USDA's physical containment measures. Moreover, these measures would ensure that commercialization of biopharm crops is channeled only into paths that are likely to protect public safety. It is inexcusable that USDA has adopted none of these proactive measures but has, instead,

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[199]Some industry estimates are that biopharmaceutical production may be a $12-14 billion industry by 2005. See, Response from Stephen H. Howell, Director of the Plant Science Institute at Iowa State University, to the BIO Guidance concerning "Plants Intended Not to Be Used for Food or Feed," available at www.grassley.senate.gov (link available on Senator Grassley's Nov. 4, 2002 press release).

[200] *See* Philip Brasher, *Iowa Denied New 'Drug' Corn*, DES MOINES REG., Oct. 23, 2002, at 1A; Philip Brasher, *Biotech Group Lifts Corn Ban*, DES MOINES REG., Dec. 4, 2002, at 1A.

[201]Iowa's Senator Chuck Grassley led the campaign to get this committment revoked stating:" BIO is responding to the demands of special interest, not the demands of science. I'll continue to work to ensure that Iowa is not unjustly left out of corn-based pharmaceutical crop production," See, Press Release, Senator Chuck Grassley, *Grassley continues Efforts to Support Biotech Crop Production in Iowa* (Nov. 4, 2002), available at www.grassley.senate.gov.

contented itself with waiting until biopharm crops are ready for field testing and then imposing physical containment measures.

When protection of the food supply rests entirely on physical containment measures, there are at least four likely routes for these biopharmed non-food crops to enter the human food supply: 1) direct human action intentionally or negligently contaminating the food supply; 2) volunteer plants contaminating the next year's food crops; 3) pollen drift contaminating nearby food crops; and 4) improperly cleaned farm machinery or spilled seeds contaminating food crops. All four have already occurred with experimental GM or biopharm crops, and unless steps are taken, all surely will occur again.

Under the Plant Protection Act, USDA has responded piecemeal to well-developed proposals upon which companies have already spent a great deal of money. Under such circumstances, and constrained further by its tenuous lines of authority, USDA has not sufficiently considered overarching concerns. This regulatory hole is undeniably attributable to the agencies hopelessly conflicted mission, but is made worse by the absence of any laws directed specifically at regulating biotechnology.

The Framework's requirement that biotechnology be regulated under existing law, seriously hampers agency ability to propose and enforce needed rules. Regulators have tried to cobble together a scheme by taking bits and pieces of a whole series of laws drafted to confront other problems. In doing so, they have already stretched existing laws almost beyond recognition,[202] and all for nought. The regulatory scheme created by these contortions is simply not up to its task

The status quo is unsafe and unacceptable. We must not wait for a tragedy before taking the sensible steps that will ensure safe exploration of this technology. We need laws and

[202]For example, FDA has expressed its intent to regulate transgenic salmon as an animal drug under FFDCA. Aside from the problem that this claim of regulatory authority contorts the statutory language past all reasonable limits, this interpretation leaves gaping regulatory holes. For example, it is unclear whether FDA has authority to consider ecosystem harms. See, *Future Fish: Issues in Science and Regulation of Transgenic Fish*, available at http://pewagbiotech.org/research/fish/.

regulations that are directly on point, and that clarify the scope of regulators' authority to supervise earlier stages in the biopharm crop development process in order to require biological containment measures. At least as important, specific agencies need express delegations of clear regulatory responsibilities and goals.[203] USDA has used tenuous lines of authority to make important, and highly politicized policy decisions about a technology on the frontiers of science; and to make these decisions with little or no scientific information, and in a political climate strongly favoring technology. It is perhaps not surprising that, under the circumstances, the agency has been wholly responsive rather than actaing proactively. Without direct congressional action on this front, we can expect only more of the same-- the agency will continue making post hoc approval decisions that do not, and indeed cannot incorporate some of the most serious concerns about this new technology.

The only way out of this conundrum is for Congress to take charge and pass new laws directly addressing the problems surrounding biopharming. These laws should recognize the unique nature of biopharmed crops, and require development of a special regulatory system devoted to the specific challenges posed by the new technology. A statutory presumption against the use of food crops would go a long way towards curing the flaws identified in this article. This presumption would not be irrebuttable, but could be overcome only upon a showing that use of non-food crops is technically infeasible and that the public interest at stake is important or compelling. The biopharm crop developer should have the burden of proof on each of these points. Such a rule would permit biopharming in food crops if it is truly in the public's interest, but would not permit private commercial assessments of profitability to supplant significant public safety concerns.

The existing scheme leaves the public exposed and vulnerable. There is no way to impose

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[203]C.f., Thomas P. Redick, Biopharming, Biosafety & Billion Dollar Debacles: Preventing Liability for Biotech Crops, 8 Drake J. Agric. L. 115 (proposing contract based stewardship regime in lieu of new regulations.) In light of the signal failure of such regimes to date, they are a slender reed upon which to balance food safety and the fate of the United States' multi-billion dollar commodity export business. See also, Marcia Ellen DeGeer, Comment: Can Roundup Ready Seeds Every Be Corralled?: Restraining Genetic Drift Through Criminal Sanctions, 29 N.ENG.J.C.C.C. 255 (2003) (arguing for use of criminal penalties to deter genetic drift).

USDA's post hoc physical containment measures in a way that will actually be protective of the public health without also creating a cost-prohibitive and burdensome oversight system. And, even were USDA to actually institute such a detailed and omnipresent system, physical containment simply cannot be done. Cross-pollination will occur; farmers will fail to follow planting requirements; accidents will happen. Use of food crops for biopharming therefore guarantees that at least low levels, and possibly significant quantities, of biopharmed proteins will wind up in human foods. There is no Plan B–no backup means for uncontaminating the food supply. Indeed, once these crops are developed and marketed, the only possible restrictions will be extremely costly to implement and none of them can successfully protect the nation's food supply from contamination.[204]

IV. CONCLUSION

Working within a regulatory framework largely unfettered by environmental, or health and safety considerations, it is perhaps not surprising that biotech developers focused on corn as the most immediately cost effective vehicle for their project.[205] Corn is well characterized and the growing cycle is well-understood. And, of course, there is the influence of corn boards and lobbies. With few regulators raising concerns about cross-fertilization and commingling, developers spent years and large sums of money developing potential corn biopharm products. Now agricultural economists pose the question "*what is the most efficient level of biosafety obtained for the cost of*

[204]For example, the National Research Council unambiguously concluded that, with regard to producing human monoclonal antibodies in plants, "[i]t would be essential to grow these plants in restricted locations," meaning isolated from food crops. Trangenic Plants at p. 228.

[205]See, e.g., Glynis Giddings, et al., *Transgenic plants as factories for biopharmaceuticals* , 18 NATURE BIOTECHNOLOGY 1151,1152-54 (Nov. 2000) (noting that many biotech companies use corn because of the economics of production).

regulation incurred in the current system?"[206] This is not the proper question. The current regulatory system is not etched in stone. This article identifies a number of regulatory measures that would permit the development of this technology while providing far more protection for the food supply.

Decisionmaking about food safety necessarily entails balancing competing values and interests,[207] but irreversible tradeoffs of this magnitude ought not be lightly made. It may be that the public is willing to accept this trade–the prospect of inexpensive and plentiful therapeutics and plastics may be attractive enough to accept the threat of contaminated food. But, such a fundamental and irrevocable choice should be the product of a public discussion[208] and decisionmaking process,[209] not the byproduct of private economic ordering. While economic efficiency is an important factor in regulation,[210] there is an even more important preliminary question that seems never to have been asked–are there directions of research that should be

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[206]See, e.g., José Falck Zepeda, Joel Cohen and John Komen, BIOTECHNOLOGY, BIOSAFETY AND REGULATORY COSTS, available at http://www.economia.uniroma2.it/conferenze/icabr2003/abstract/Regulation%20of%20the%20biotech%20sector/Zepeda%201.doc.

[207]For a general description of food safety decisionmaking, see Vern R. Walker, *Some Dangers of Taking Precautions Without Adopting the Precautionary Principle: A Critique of Food Safety Regulation in the United States*, 31 Envtl. L. Rep. 10040 (Jan. 2001).

[208]See, Christopher H. Schroeder, *Deliberative Democracy's Attempt to Turn Politics into Law*, Law & Contemp. Probs., Summer 2002 (for a discussion of the hurdles to having such a conversation).

[209]For a discussion of how such decisionmaking could, or ought to take place, see Daniel A. Farber, ECO-PRAGMATISM 39-42 (1999).

[210]Cost benefit analyses are now *de rigeur* for almost all agency decisionmaking. See Regulatory Planning and Review, Executive Order 12,866, 58 Fed. Reg. 51,735 (September 30, 1993). As a tool, cost-benefit analysis can be extremely informative. For questions like the ones posed in this article, where the benefits are inchoate and the risks are probabilistic, the tool of risk benefit analysis is too often distorted or manipulated in the hands of ideologically or economically interested actors. For a recent critique of what passes for reasoned analysis in the world of cost-benefit balancing, see Frank Ackerman, Liza Heizerling, Pricing the Priceless: Cost Benefit Analysis of Environmental Protection, 150 U.Pa.L.R. 1553 (2002).

categorically excluded at the beginning in order to ensure that the fruits of the research can be grown without compromising the security of the food supply?

Pressure finds the weakest spot. Had the biopharming developers been forced to internalize these public health concerns during the development process, the products now being readied for market would have confronted and solved the problems, either through use of non-food crops as a production vehicle or through an as-yet undeveloped extensive and elaborate system of biological and geographic safeguards like those detailed in this article. The status quo would have been protective. Instead, developers were free to build a status quo that did not include consideration of these basic human health concerns.

When baseline protective measures are added after the fact, they are always too little, too late. Even worse, the measures are viewed as changing a status quo and "adding" costs. All too often, these protective measures are considered regulatory red tape–unnecessary hurdles placed between developers and their just rewards by an unresponsive and incompetent bureaucracy. Under those circumstances, developers push for compromise on the measures intended to protect public health.

Let me be clear–there are real potential advantages to this technology. It could provide a cost-effective means to produce desperately needed therapeutic proteins. Plants are not known to harbor bacterial or viral pathogens that infect humans or animals, which means that the purification risks are reduced.[211] It is simply much less likely to contaminate a batch of plant-grown pharmaceuticals accidentally with a human pathogen. After mad cow disease, this concern is a pressing one. Grains are also easy to transport and store. Finally, the technology could ultimately result in needle-free vaccine delivery systems that do not require refrigeration or the participation of trained medical professionals.[212] Thus biopharmed vaccines might be particularly suitable for use

[211]S.J. Streatfield, et al., *Plant Based Vaccines: Unique Advantages*, 19 Vaccine at 2748 (2001).

[212]Id.

in the developing world, and could make a reality of the dream of universal vaccination.

Without adequate safeguards, however, this technology poses imminent risks that might dwarf those benefits. It all comes down to the fact that biopharmed corn and other crops are emphatically not for consumption as food but are indistinguishable from crops intended for human consumption. As such, biopharming really does pose new and fundamental safety challenges. Answering those challenges will require concentrated effort and significant investment from the regulatory agencies and the regulated community. Unfortunately there is little to suggest a real commitment to building the sort of infrastructure needed to safely grow these crops. The specter of StarLink corn and ProdiGene is hovering. The next violation may not be caught in time, and the next crisis might not be so benign.

The integrity of the United States' food supply is at stake. With a clear likelihood of contamination, and no evidence that these crops are safe to consume, even in low levels, permitting commercial development of these products cannot be justified as scientifically sound or as a reasonable assessment of the costs and benefits. And, with the European Union, Japan, and Korea (our major grain commodity partners) establishing threshold tolerance levels for GM contamination, the United States' commodities export markets face potentially cataclysmic risks.

These failures to address the problem of contamination and commingling become even more critical now that the Cartagena Protocol on Biosafety has entered into force.[213] Article 10 of the Protocol gives states the power to refuse import of the products of biotechnology in order to avoid or minimize adverse effects on human health or the conservation and sustainable use of

[213]The text of the Cartagena Protocol on Biosafety is available at: http://www.biodiv.org/biosafety/protocol.asp . The Protocol entered into force on September 11, 2003 following the 50th ratification, by Palau. There are currently 60 members of the Protocol, including the European Union and other significant United States trading partners like Mexico. Cartagena Protocol on Biosafety, Status of Ratification and Entry into Force, available at: http://www.biodiv.org/biosafety/signinglist.aspx?sts=rtf&ord=dt.

biologicaldiversity.[214] It is hard to imagine anything more likely to trigger a refusal to import under the Cartagena Protocol than undetectable commingling of industrial or pharmaceutical crops containing non-food proteins with export food crops.

[214]Id. Section 11.