SELLING THE PHARM: THE RISKS, BENEFITS, AND REGULATION OF BIOPHARMACEUTICALS

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INTRODUCTION

This past 2003 to 2004 flu season began earlier than usual and garnered widespread media attention as the illness claimed more and more lives across the country.[1] News outlets began reporting long lines of people waiting for diminishing supplies of flu vaccines.[2] Midway into the flu season, several regions reported complete shortages of the vaccine, and some parents drove hours to hospitals in hopes of obtaining injections for their children.[3]

I hate shots. Like many others, I made the deliberate choice not to get a flu vaccine in October.[4] By December, panicked by media reports, I attempted to get one at local infirmaries, only to learn that there was a shortage of the vaccine in Northern California as well.[5] Of course, for the first time in years, I got the flu. My fear of a quick but painful injection resulted in me being bedridden for over a week.

For those who are afraid of anything in the form of a needle or pill, there may be a future solution. Soon, rather than getting an injection, one will be able to eat a candy bar containing the vaccine, which is just as effective but much less painful.[6] Or, after battling a nasty stomach bug, a

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[1] *See* Thomas H. Maugh, *Aggressive Flu Strain Hits Early and Hard*, L.A. TIMES, Dec. 5, 2003, at A1; *see also* Rob Stein, *Worst of Flu Epidemic May be Over, CDC Says*, WASH. POST, Jan. 9, 2004, at A03 (noting that flu season emerged sooner than usual and hit hard, especially in Western United States); Jia-Rui Chong, *Flu Patients Inundating Southland Ers*, L.A. TIMES, Dec. 20, 2003, at B1 (reporting fourth flu-related death in Southern California).

[2] *See, e.g., CDC Opens Emergency Center for Flu*, L.A. TIMES, Dec. 20, 2003, at A29 (reporting shortages of flu vaccine in many areas as demand of vaccine outpaced supply); Bruce Alpert, *Bill Targets Flu Vaccine Shortages*, TIMES-PICAYUNE, Jan. 29, 2004, at 10 (stating that companies produced twelve million fewer doses of flu vaccine than previous year, resulting in widespread shortages).

[3] *See* Sarah Kershaw, *Flu in the West Closes Schools but Fills Clinics,* N.Y. TIMES, Dec. 12, 2003, at A1; *see also* Lisa Richardson et. al, *With Flu Season's Fear Factor, Vaccine Supply Just About Shot*, L.A. TIMES, Dec. 13, 2003, at B1 (describing some clinics using entire season of vaccine in days, while others have waiting lists of more than fifty families).

[4] *See, e.g.,* Jane E. Allen, *Is it a cold or the flu?*, L.A. TIMES, Dec. 22, 2003, at F3 (noting that health officials have difficult time persuading people to get flu shot); Richardson et. al, *supra* note 3 (revealing that at least one Southern Californian waited until media coverage to get flu vaccine, only to discover that family health center was out of vaccine).

[5] *See, e.g.,* Chong, *supra* note 1, (noting that flu bug spread sooner and more rapidly in Northern California); Richardson et al., *supra* note 3, (reporting that flu season peaked early in Sacramento).

[6] *See, e.g.,* Andrew Pollack, *New Ventures Aim to Put Farms in Vanguard of Drug Production*, N.Y. TIMES, May 14, 2000, at 1 (reporting research and development of edible vaccines which people could eat genetically engineered foods to protect themselves from disease) [hereinafter Pollack, *New Ventures*]; Andrew Pollack, *U.S. Imposes Stricter Rules for Genetically Modified Crops*, N.Y. TIMES, Mar. 7, 2003, at A23 (noting that biopharming may allow development of vaccines that can be eaten in-

person will dine on a potato containing a viral protein that will prevent them from becoming sick with the same virus in the future.[7] Or, for the wary consumer averse to edible vaccines, the widespread availability of inexpensive medicines presents a favorable alternative to the current inaccessibility of many drugs due to high costs and insufficient supplies.[8]

The production of genetically altered plants that contain pharmaceuticals may become the new trend in farming.[9] Advances in biotechnology have led industry leaders to tout this emerging technology as having the capacity to produce life-saving therapeutics.[10] Some biotechnology companies have planted crops genetically engineered to produce pharmaceuticals, antibodies, and industrial enzymes.[11] Also called "biopharming" or "molecular farming," this is poised to be the next wave in agricultural biotechnology.[12]

As with any new technology, it is important for proponents and opponents alike not to approach it with either "blind faith"[13] or "irrational fear."[14] This paper assesses the primary issues surrounding biopharming

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stead of injected) [hereinafter Pollack, *Stricter Rules*]; Andrew Pollack, *Vaccine Delivered by Fork, Not Needle*, N.Y. TIMES, May 14, 2000, at 26 (describing potentials of edible vaccines by example of eating candy bar to fight disease rather than traditional method of injection) [hereinafter Pollack, *Vaccine Delivered by Fork*].

7 *See, e.g.,* Pollack, *Vaccine Delivered by Fork*, supra note 6 (relating human clinical test in which people ate potatoes to prevent vomiting and diarrhea virus).

8 *See* Pollack, *New Ventures*, *supra* note 6; Biotechnology Industry Organization, *Advantages of Plants to Produce Therapeutic Proteins*, *at* http://www.bio.org/pmp (last visited Apr. 1, 2003); Union of Concerned Scientists, *Pharm and Industrial Crops: The Next Wave of Agricultural Biotechnology*, *at* http://www.ucsusa.org/pharm/pharm_open.html (last visited Mar. 26, 2003); *see also* Lisa J. Dry, *The Case for Plant-Made Pharmaceuticals*, BIO NEWS, Apr./May 2002, *at* http://www.bio.org/pmp. (last visited Mar. 13, 2004) (reporting that industry faces critical manufacturing shortages that biopharming may alleviate).

9 Pollack, *New Ventures*, *supra* note 6.

10 *See, e.g.,* Biotechnology Industry Organization, *Plant-made Pharmaceuticals and Genetically Enhanced Foods*, available at www.bio.org (last visited Jan. 3, 2004) (pledging that new advances in biotechnology have made it possible to use plants to produce life-saving therapeutic proteins). The Biotechnology Industry Organization is comprised of more than one thousand biotechnology companies, academic institutions, state biotechnology centers, and related institutions.

11 *See* ERIC S. GRACE, BIOTECHNOLOGY UNZIPPED: PROMISES & REALITIES 126 (1997).

12 *See generally id.* at 125-26 (1997) (describing molecular farming enterprise); BILL FREESE, MANUFACTURING DRUGS AND CHEMICALS IN CROPS: BIOPHARMING POSES NEW THREATS TO CONSUMERS, FARMERS, FOOD COMPANIES AND THE ENVIRONMENT, 6 (July 2002), *available at* www.foe.org/biopharm (last visited Mar. 16, 2003) (defining biopharming).

13 PHARMING THE FIELD: A LOOK AT THE BENEFITS AND RISKS OF BIOENGINEERING PLANTS TO PRODUCE PHARMACEUTICALS 3 (July 2002), *available at* http://pewagbiotech.org/events/0717/ConferenceReport.pdf (last visited Mar. 16, 2003).

14 *Id.*

and its regulatory framework, focusing on biopharming as it relates to pharmaceuticals. Part I provides a background for understanding biotechnology, including a description of the current practice of producing biopharmaceuticals in a laboratory setting. Part II describes the testing of growing medications and other compounds in plants, and addresses the potential advantages of and concerns about this developing practice. Part III documents the regulatory structure and the new permit conditions of biopharm field sites. Part IV analyzes biopharming regulations and suggests prospective changes to ensure risk prevention without stifling innovation and growth in this field.

I. BACKGROUND

Biotechnology involves using science to utilize and alter living things in order to make products or provide beneficial services.[15] Humans have modified living organisms for centuries, such as selectively breeding desirable crops and animals.[16] Now, with new knowledge and understanding of the structure of deoxyribonucleic acid (DNA), scientists are able to genetically manipulate organisms through cellular and molecular structures, thus using organisms' valuable traits more precisely than before.[17]

Every living organism is composed of cells, which are microscopic units of living material.[18] A cell is the simplest living system that can exist independently.[19] DNA is essentially the "master molecule" of the cell and builds up the amino acid chain of a protein.[20] As the genetic code of all cells, DNA carries hereditary information.[21] Ultimately, it is responsible for the physical characteristics of all living creatures.[22] Every living organism is built and functions on molecules.[23] The molecules in DNA

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15 *See* GRACE, *supra* note 11, at 2; LISA YOUNT, BIOTECHNOLOGY AND GENETIC ENGINEERING 119 (2000).

16 *See* Jonathon H. Adler, *More Sorry Than Safe: Assessing the Precautionary Principle and the Proposed International Biosafety Protocol*, 35 TEX. INT'L L.J. 173, 175 (2000); *see also* G.J. PERSLEY ET AL., BIOSAFETY: THE SAFE APPLICATION OF BIOTECHNOLOGY IN AGRICULTURE AND THE ENVIRONMENT 2 (1992) (noting that biotechnology is not new science but rather term given to advances made in genetics).

17 *See, e.g.*, GRACE, *supra* note 11, at 1-30 (describing benefits of using new modern biotechnology techniques to take advantage of biological processes).

18 Dan L. Burk, *Symposium: A Biotechnology Primer*, 55 U. PITT. L. REV. 611, 612 (1994); YOUNT, *supra* note 15, at 120.

19 *See* YOUNT, *supra* note 18, at 120.

20 BURK, *supra* note 18, at 612-23.

21 CAROLYN BLOCH, PLANT AGRICULTURE: FEDERAL BIOTECHNOLOGY ACTIVITIES 3 (1986); GRACE, *supra* note 11, at 14; YOUNT, *supra* note 15, at 121; PLANT PRODUCTS AND THE NEW TECHNOLOGY 205 (K.W. Fuller & J.R. Gallon eds., 1985).

22 BURK, *supra* note 18, at 613.

23 GRACE, *supra* note 11, at 21.

strands form genes, which essentially instruct cells how to assemble proteins.[24]

Genes consist of smaller molecules called amino acids.[25] A gene's function is to produce proteins, which are "the very foundation of living systems."[26] Proteins, which consist of smaller molecules called amino acids, perform essential functions in cells, including acting as enzymes, fighting infections, and making important structural materials such as muscle fiber.[27] For example, there are over 30,000 types of proteins in the human body, and each has its own specific purpose.[28]

Innovations in technology and improved understanding of the relationship between proteins and genetic instructions enable scientists to develop more commercially useful products.[29] Beginning in the 1970's, scientists learned how to cut and splice DNA, and thus introduce genes from one organism into another completely different organism.[30] Such alterations are integrated into the genetic code of the modified organism and can be inherited when the modified organism reproduces.[31] This direct manipulation of genetic information and gene transfer to produce new microorganisms became known as "genetic engineering."[32] "Because the genetic code is universal, almost any cell in any organism can 'read' a gene and translate it into the relevant protein."[33] Through genetic engineering,[34] scientists can introduce new traits to organisms that older techniques, such as crossbreeding, could not.[35]

The combination of genetic material from two different sources is often called "recombinant DNA" (rDNA).[36] The resulting organisms, which have genes from two or more species are called "transgenic" or

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[24] DANIEL POLLAK, CALIFORNIA'S BIOSCIENCE INDUSTRIES: OVERVIEW AND POLICY ISSUES 7 (2002).

[25] GRACE, *supra* note 11, at 22, 30; BLOCH, *supra* note 21, at 3; POLLAK, *supra* note 24, at 7.

[26] GRACE, *supra* note 11, at 22; BLOCH, *supra* note 21, at 3; POLLAK, *supra* note 24, at 7.

[27] BURK, *supra* note 18, at 612; YOUNT, *supra* note 18, at 127; GRACE, *supra* note 11, at 21; POLLAK, supra note 24, at 7; BLOCH, *supra* note 21, at 3. An enzyme is a protein that catalyzes essential chemical reactions in living cells. YOUNT, *supra* note 15, at 7.

[28] GRACE, *supra* note 11, at 22.

[29] GRACE, *supra* note 11, at 24-25; BLOCH, *supra* note 21, at 4.

[30] POLLAK, *supra* note 24, at 7; Adler, *supra* note 16, at 176.

[31] POLLAK, *supra* note 24, at 7.

[32] YOUNT, *supra* note 18, at 123.

[33] GRACE, *supra* note 11, at 30.

[34] "Gene splicing is a common term for insertion of one or more genes from one species into the genome of another [and is a] synonym for recombinant DNA technology." YOUNT, *supra* note 18, at 123.

[35] POLLAK, *supra* note 18, at 7.

[36] YOUNT, *supra* note 18, at 123.

"genetically modified" organisms.[37] In biotechnology, rDNA is created in a laboratory. While biotechnology includes traditional crossbreeding, using rDNA techniques to genetically modify organisms is the form of biotechnology at the heart of most debates about increased regulation.[38]

A. Genetically Modified Organisms and Biopharmaceuticals

Recombinant DNA technology has been a primary focus of the agricultural biotechnology industry.[39] Because the basic techniques of rDNA technology are essentially the same regardless of which organisms are being studied, scientists are optimistic about the potential advances of agricultural biotechnology.[40] The increased precision of modern biotechnology processes makes the characteristics of products easier to predict, and greatly accelerates the rate of scientific progress.[41] However, the extensive potential power of biotechnology and the seemingly infinite number of possible new products has led to concerns about the possible risks these techniques present to humans and the environment.[42]

Thus far, industry and media attention has focused on genetically engineered food issues and agricultural biotechnology.[43] After a relatively quiet arrival on the market, "genetically modified" (GM) foods have become the subject of heated public debate. Events such as the controversial StarLink corn incident, in which GM corn seeds used for

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37 POLLAK, *supra* note 24, at 7; YOUNT, *supra* note 18, at 130; *see also* Richard A. Repp, *Comment: Biotech Pollution: Assessing Liability for Genetically Modified Crop Production and Genetic Drift,* 36 IDAHO L. REV. 585, 588 (2000) (noting that GMOs are now created by inserting genetic material from one species into another, and now account for more than thirty-five percent of all corn, fifty-five percent of all soybeans, and nearly half of cotton produced in the U.S.).

38 ADLER, *supra* note 16, at 4.

39 BLOCH, *supra* note 21, at 4.

40 FULLER, *supra* note 16, at 205. In agricultural research, rDNA technology involves four steps: (1) identifying, locating, and purifying the genes; (2) isolating the gene from the others on the chromosome; (3) constructing vectors to deliver the genes; (4) cloning, duplicating, or inserting the gene into the host cell. BLOCH, *supra* note 21, at 4.

41 PERSLEY, *supra* note 16, at 3-4.

42 *Id.* at 4.

43 *See, e.g.,* Lizette Alvarez, *Consumers in Europe Resist Gene-Altered Foods*, N.Y. TIMES, Feb. 11, 2003, at A3 (noting Europeans' staunch rejection to G.M. food); Danna Harman, *Some Africans prefer hunger to a diet of gene-altered corn*, CHRISTIAN SCI. MONITOR, Nov. 14, 2003, at 12 (reporting that genetically-modified foods are rotting in storehouses in Zambia because they believe such food poses health risks to people); *Monsanto Gift May Boost Altered Foods; Biotechnology: Firm's Offer of Licenses for Genetically Modified Rice Could Change Perceptions*, L.A. TIMES, Aug. 5, 2000, at C2 (describing potential benefits of "golden rice," G.M. rice which contains extra vitamin A); *see also U.N.'s Annan Urges 'Green Revolution' in Africa*, N.Y. TIMES, at www.nytimes.com/reuters/international/international-food-africa-annan.html?pagew (last visited Feb. 19, 2003).

animal feed were inadvertently mixed with human corn, and the European rejection of GM crops, have generated controversy over the safety of GM foods.[44]

There are important distinctions between genetically engineered food crops and biopharmed crops.[45] Biotechnology has developed food crops that can resist pests and disease, tolerate herbicides, or survive cold weather, droughts, and other environmental strains. Alternatively, molecular farming aims to develop crops genetically modified to produce drugs, industrial chemicals, fuels, plastics, medical products, and other materials.[46] Biopharming is still in the experimental stage and has yet to be commercialized but research and development are progressing quickly, especially with plant-based pharmaceuticals.[47] This has led to heightened interest from environmental groups and consumer advocates who have expressed concerns about containment and safety, especially as the public has grown more apprehensive about GM crops.[48]

Drugs produced through biotechnology are called "biopharmaceuticals."[49] Perhaps the most commercially important application of biotechnology is the creation of genetically engineered organisms to produce medicines. This is typically done using cell cultures, which involves growing cells under laboratory conditions.[50] Cells can be tiny, yet powerful biological factories in a laboratory setting, and capable of manufacturing many complex proteins.[51] A gene that produces a therapeutic protein is then spliced into an artificially-grown plant, animal, or bacterial cell line.[52] The multiplying cells manufacture the protein, which is then extracted.[53] For example, inserting the human insulin gene into bacteria produced the first biotech insulin used to treat diabetes, and is now pro-

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44 *See Go Slow on Genetic Pact*, L.A. TIMES, Jan. 26, 2000, at B10 (noting growing opposition in Europe to G.M. food); *see also* Elizabeth Becker, *U.S. Threatens to Act Against Europeans Over Modified Foods*, N.Y. TIMES, Jan. 10, 2003, at A4 (reporting Bush administration's consideration of whether to file a case against European Union with World Trade Organization for its ban on G.M. food).

45 *See* Emily Gersema, More Biotech Crops; *see also,* Emily Gersema, U.S. Farmer Grow (noting that European opposition to GM and a European Union moratorium on U.S. biotech imports hasn't stopped US farmers from planting more GM crops in 2003).

46 *See* GRACE, BIOTECHNOLOGY UNZIPPED, *supra* note 11, at 125.

47 *See, e.g.,* Pollack, *New Ventures*, *supra* note 6, at 1 (reporting that consumer groups urging for heightened public awareness about biopharmed crops); Pollack, *Stricter Rules*, *supra* note 6, at A23 (stating that environmental and public interest groups are urging USDA to impose stricter rules for biopharmed crops).

48 *See* PHARMING THE FIELD, *supra* note 13, at 5.

49 POLLAK, *supra* note 24, at 11.

50 BURK, *supra* note 18, at 614.

51 POLLAK, *supra* note 24, at 7; BURK, *supra* note 18, at 614-15.

52 POLLAK, *supra* note 24, at 7.

53 POLLAK, *supra* note 24, at 8.

duced on an industrial scale.[54] Currently, manufacturers usually use Chinese hamster ovaries (CHO) to produce therapeutic proteins in fermentation tanks or bioreactors. These specialized CHO cells produce a variety of human proteins.

In 2000, 400 biopharmaceuticals were in development and 100 were on the market.[55] Biotechnology is valuable for the production of medication because it can be used to manufacture known drugs, as well as to create new therapies and vaccines.[56] Given that there are still no medications to treat or cure a variety of significant diseases, biotechnology presents an important method for developing potential treatments.[57] A growing number of treatments for diseases such as herpes, arthritis, immune system sicknesses, and infectious diseases require human and viral proteins.[58] Drug makers currently synthesize these proteins in animal cell cultures because they must be derived from living organisms.[59]

However, drug manufacturers have run into problems such as high production costs, insufficient capacity, and supply not nearly meeting demand. Production limitations related to the high costs of building bioreactors is a common problem. For example, many pharmaceuticals are brewed in fermentation tanks.[60] In order to brew more pharmaceuticals, a company must add more vats, which eventually necessitates more production plants. Building a plant is extremely expensive, costing an estimated $500 million.[61] As a result of these limitations, current manufacturing practices are incapable of fostering enough CHO cells to keep up with the demand for protein products. For example, four pharmaceutical products containing human proteins currently consume seventy-five percent of existing cell fermentation capacity.[62] This has led to pressure to explore alternative, cost-effective production methods to ensure that new treatments are developed and made available to the public.

The first wave of agricultural biotechnology proved that scientists could alter plants to produce useful traits that still function in a natural environment. For example, farmers could spray herbicide on Roundup

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54 POLLAK, *supra* note 24, at 8; GRACE, *supra* note 11, at 30.

55 POLLAK, *supra* note 24, at 11.

56 POLLAK, *supra* note 24, at 11-12.

57 *See, e.g.*, U.S. DEP'T OF AGRIC., NEW CROPS, NEW USES, NEW MARKETS 134 (1992) (stating that there still lacks specific curative agents for diseases from which nearly one-fifth of the world suffers, such as malaria, leprosy, viral diseases like AIDS, cancer, and heart disease).

58 *See* NEW CROPS, *supra* note 55, at 4.

59 PHARMING THE FIELD, *supra* note 13, at 2; Allan S. Felson, *Pharm Farming: It's Not Your Father's Agriculture*, AGRICULTURAL & ENVTL. NEWS (2002), *available at* http://aenews.wsu.edu/July02AENews/PharmFarming/PharmFarming.pdf.

60 Felson, *supra* note 59, at 2.

61 *Id.*

62 PHARMING THE FIELD, *supra* note 13, at 4.

Ready crops to kill pests while the crops thrived, immune to the pesticide. BT corn creates a toxin that kills a corn-eating insect, and is a safe and effective tool for farmers.[63] With these and other demonstrated successes, the biotechnology industry has turned to biopharming as a potential alternative of generating pharmaceuticals.

II. WHAT IS "BIOPHARMING"?

Plants and other living organisms naturally contain biopharmaceuticals, chemicals and materials that may be used for medical and diagnostic purposes. Plant compounds have historically been used in medication. For example, Aspirin's pain-relieving properties are derived from salicin, a compound in willow plants.[64] Approximately 121 prescription drugs are derived from ninety-five different plant species.[65]

Biopharming involves using biotechnology to manipulate plants' genetic codes to produce biopharmaceuticals. Scientists are developing GM crop methods for harvesting medications otherwise difficult to produce.[66] Most advances in biopharming have been in the development of plants capable of producing and storing human proteins. Farmers or processors can then extract useful enzymes and pharmaceuticals after the crop is harvested. Scientists are conducting field studies in an attempt to grow plants that also produce completely new products, such as industrial chemicals. For example, one biotechnology firm is conducting a field trial of corn that grows laccasse, which is used for adhesives and textiles.[67] Thus, research and development of biopharming has moved from the laboratories to the fields. From 1991 to 2002, the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) approved 315 open-air field trials of plants containing pharmaceuticals.[68]

A. Farming Pharmaceuticals: Growing Drugs in Plants

There are many possible advantages to producing pharmaceuticals in plants. While biopharmaceutical farms may be diminutive in size compared to crops grown for general consumption, it should be relatively easy to increase crop acreage, and hence production of the medication or

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63 *Roundup Unready*. N.Y. TIMES, Feb. 19, 2003.

64 Mary Bellis, *History of Aspirin, at* http://inventors.about.com/library/inventors/blaspirin.htm (last visited Mar. 10, 2004).

65 KAZUO N. WATANABE & EIJA PEHU, PLANT BIOTECHNOLOGY AND PLANT GENETIC RESOURCES FOR SUSTAINABILITY AND PRODUCTIVITY 211 (1997).

66 POLLAK, *supra* note 27, at 12; Burk, *supra* note 18, at 624.

67 FREESE, *supra* note 12, at 33.

68 Bill Freese, *Secret U.S. Biopharms Growing Experimental Drugs*, *available at* ens-news.com/ens/jul2002/2002-07-16-05.asp (last visited March 4, 2003).

protein being grown.[69] The acreage of field sites thus far has been relatively small. For example, in 2002, the APHIS authorized thirty-four field test sites totaling 130 acres.[70] Most of these test sites were less than five acres.

Another benefit of molecular farming is that there are established methods for efficient harvest, transport, storage and processing of certain crops.[71] This information will be beneficial in shaping regulations that oversee the use of various food crops for pharmaceuticals. Nonetheless, the most important benefit of biopharming is that it potentially represents a more cost-effective way of producing pharmaceuticals.[72] As the conventional bioreactor methods are limited due to the high costs associated with manufacturing facilities and capabilities, plants may present a significantly cheaper method of mass-producing the same pharmaceuticals.

Industry leaders argue that if biopharming is able to safely and cost-effectively produce medicines, more capital can be invested in the research and development of new therapeutics.[73] Biopharming also poses the potential for faster and more flexible manufacturing than do current practices since farmers can more easily increase or decrease crop plants in response to the market. Theoretically, more new drugs could become available sooner.

Biotechnology companies are also touting the important societal benefits of biopharmaceutical plants, including lower drug prices, increased availability of medication, and inexpensive vaccines for developing countries. Molecular farming does not involve the same costly investments as current practices.[74] Because transgenic plants can store high yields of recombinant proteins, production costs for growing pharmaceuticals should be significantly lower compared to cell cultures and bacterial fermentation. The biotechnology industry admits that there is not enough evidence to prove that biopharmaceuticals will be a viable and cost-effective alternative to current processes.

However, in some instances, the potential cost-savings could be significant. Some biotechnology companies have estimated that drug prices

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[69] CHEMICALS VIA HIGHER PLANT BIOENGINEERING 128 (Fereidoon Shahidi et al. eds., 1999).

[70] Field Testing of Plants Engineered To Produce Pharmaceutical and Industrial Compounds, 68 Fed Reg. 11337 (Mar. 10, 2003) (to be codified at 7 C.F.R. pt. 340).

[71] CHEMICALS VIA HIGHER PLANT BIOENGINEERING, *supra* note 70, at 128.

[72] *Id.* at 128, 150 (arguing that plants can be grown cheaply because all they need is water, carbon dioxide, sunlight, nitrogen, and small amounts of other minerals).

[73] Biotechnology Industry Organization, *Consumer Benefits of Plant-Made Pharmaceuticals*, *available at* www.bio.org (last visited February 3, 2004).

[74] *See, e.g.*, CHEMICALS VIA HIGHER PLANT BIOENGINEERING, *supra* note 70, at 127-28 (contending that use of transgenic plants for large-scale production of pharmaceutical protein can be one of most economical approaches).

could be ten to one hundred times lower than current prices because of the expected cost savings on infrastructure and production. For example, it currently costs an average of $400,000 a year to treat a person with Fabry's disease.[75] Biotechnology companies estimate that this cost could potentially drop to $40,000 per year. Another example is the expense of producing 1000 kilograms of human antibodies using current CHO practices, which amounts to approximately $100 to $175 per gram.[76] Some estimates predict that biopharm plants could produce the same amount for $15 to $190 per gram.[77] Proteins that can be grown in corn, which currently cost $1,000 per gram, are estimated to cost between $10 and $100.[78] Similarly, twenty-six tobacco plants could make enough glucocerebrosidase, one of the most expensive medications in the world, to treat a person with Gaucher's disease for an entire year.[79] Thus, industry may potentially be able to grow medication that is too expensive to produce through current biotechnology procedures. In addition, the biotechnology industry hopes to develop oral vaccines, which could greatly benefit developing countries.

B. Current Biopharmaceutical Crops

Perhaps one of the biggest controversies surrounding molecular farming is the use of food crops to produce pharmaceuticals in open-air field trials. With the exception of tobacco, the primary candidates for biopharm plants are food crops, including corn, potato, rice, safflower, and soybean. Biotechnology companies assert that they chose these crops because they have been studied in detail with respect to pollina-

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[75] Union of Concerned Scientists, *What Are the Potential Societal Benefits of Pharm and Industrial Crops?*, *at* www.ucsusa.org/pharm/pharm_benefits.html (last visited March 2, 2003). Fabry's disease is a fat storage disorder caused by an enzyme deficiency. *See* http://healthlink.mcw.edu/article/921727118.html (last visited March 2, 2003). Without this fat-metabolizing enzyme, fats built to extremely high levels inside organs. *Id.* This causes carriers to suffer a number of ailments, such as burning sensations in their hands and feet, debilitating pain. *Id.* Carriers are at a high risk for strokes, heart attacks, and kidney damage. *Id.* On April 25, 2003, the FDA approved a genetically-engineered version of the missing enzyme. *See New Treatment for Fabry's Disease*, *at* http://abclocal.go.com/wpvi/news/42503-fabrys.html (last visited March 2, 2003).

[76] PHARMING THE FIELD, *supra* note 13, at 8.

[77] *See id.* at 6.

[78] Union of Concerned Scientists, *Why Are Companies Producing Drugs and Industrial Chemicals in Crops*, *available at* http://www.ucsusa.org/pharm/pharm_why.html (last visited March 5, 2003).

[79] Union of Concerned Scientists, *supra* note 75. Gaucher's disease is an inherited, enzyme deficiency disorder. *See* Gaucher Disease, *at* http://www.gaucher.org.uk. (last visited Mar. 10, 2004). Symptoms include anemia, fatigue, a tendency to bleed, and bone pain. *Id.*

tion, genetics, seed dormancy, and weediness.[80] This allows industry to better control factors that could lead to inadvertent mixing with other plants and contamination with non-biopharm food crops. Thus, biotechnology companies are using crops with which they are most familiar, and about which they have the most data, and can best control the system.[81] Using familiar crops with established techniques allows industry to better control problems such as cross-pollination.

Corn is the most popular crop for field tests, accounting for over two-thirds of the crops used for biopharm plantings.[82] Other crops include soybeans, tobacco, and rice. Two test trials in 1991 and 1996 involved growing tobacco plants to harvest Trichosanthin, a root plant used in China to induce abortions. Trichosanthin shows some promise as an AIDS treatment but also causes severe immune system reactions when administered repeatedly.[83] In January 2004, a biotechnology firm based in Sacramento, California proposed growing 130 acres of rice to produce anti-microbial proteins for use in treating infections in infants.[84]

C. Concerns About Molecular Farming

While there are many concerns about the potential hazards involved in using plants to produce pharmaceuticals, there are uncontrollable factors in farming any crop. With biopharming, the risks are increased because the plant itself will contain products such as proteins or medicines. Some plants, such as corn containing the industrial enzyme trypsin, are known human allergens.[85] Concerns involve environmental impacts as well as human health risks. Some of the most serious hazards associated with molecular farming include the danger that biopharmed crops will mix with crops grown for human consumption and that biopharmed crops will cross-pollinate with human food crops. These risks have led some interest groups to file petitions with the United States Department

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[80] *Pharm Farming*, *supra* note 60, at 9.

[81] PHARMING THE FIELD, *supra* note 13, at 13.

[82] FREESE, *supra* note 12, at 1.

[83] Health Canada, the Canadian equivalent to the U.S. F.D.A., issued a warning against ingestion of medications containing trichosanthin because of the harm it causes to embryos, immune systems, and the potential for severe allergic reactions. *See Warning Not to Consume Traditional Chinese Medications Containing Tricosanthes and Indicated for Use in Children, at* http://www.hc-sc.gc.ca/english/protection/warnings/2001/2001_22e.htm (last visited Mar. 4, 2004). Interestingly, the U.S.D.A. has ruled that there is no evidence of adverse human health impacts from trichosanthin. Genetically Engineered Crop Health Impacts Evaluation — GAPS Analysis, *at* www.foe.org/safefood/gapseval.pdf) (last visited Mar. 4, 2004).

[84] Mike Lee & Edie Lau, *Biotech Company Cultivates New Field, But the Genetically Altered Pharmaceutical Rice it Wants to Grow Has Raised Fears*, SACRAMENTO BEE, Jan. 25, 2004, at A1.

[85] *What Is Biofarming?*, 12 Global Pesticide Campaigner (2002), *available at* www.panna.org/resources/gpc/gpc_200212.12.3.10.dv.html (last visited Mar. 15, 2003).

of Agriculture (USDA) demanding that the agency ban biotechnology companies from planting biopharmaceuticals.[86]

1. Cross-Pollination Concerns: Prudence or Panic?

One of the primary fears about growing pharmaceuticals in plants is the potential for biopharm crops to cross-pollinate with other plants, namely crops intended for food and feed. Pollination involves the transfer of pollen within a flower or between flowers.[87] In corn, cross-pollination occurs when wind carries corn pollen as it falls from tassels. When corn tassels release pollen, a fog of pollen grains can envelope the surrounding vegetation.[88] Given corn's tendency to pollinate, many critics of biopharming have focused on its widespread use in the pharmaceuticals industry. Several have suggested that the Animal and Plant Health Inspection Service (APHIS) prohibit biopharming in Corn Belt states, or outlaw the use of corn in field test trials completely.

Is the concern over cross-pollination justified? Critics of biopharming, and of GM crops in general, "made it look like there was going to be a cloud of genetically engineered pollen flying all over the state."[89] However, studies have demonstrated that there may not be cause for such concerns. For example, there has yet to be a documented case where heavy exposure to pollen led to hybridization of genes resulting in a problematic, viable plant. Extensive experiments with temporal, physical, and biological barriers to prevent unintentional gene transfers show that the risk is minimal, at best.[90] A study at the University of Maine concluded that the chance of cross-pollination between corn plants is small when crops are in close proximity to each other.[91] With increased distance between crops, this risk quickly drops to zero. Illustrating a worst-case scenario, conventional corn was planted 100 feet away, downwind, from GM corn. The results revealed that there was a one percent chance of cross-pollination in the first six rows when hybrid corn was grown 100 feet downwind from GM corn. In the middle six rows, the

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[86] The GE Food Alert Campaign Center, *at* www.gefoodalert.org/pages/home.cfm. (last visited Mar. 10, 2004).

[87] Mississippi State University Extension Service, Vegetables: Pollination, *available at* http://msucares.com/lawn/garden/vegetables/pollination (last visited Mar. 10, 2004).

[88] CONFERENCE REPORT: WORKSHOP ON SAFEGUARDS FOR PLANNED INTRODUCTION OF TRANSGENIC CORN AND WHEAT 8 (L. Val Giddings et al. eds., 1990) *at* www.aphis.usda.gov/ppq/biotech/pdf/workshop/corn-wheat.pdf (last visited March 20, 2003).

[89] Steve Groff, *Study finds little cross-pollination*, *available at* http://www.sare.org/htdocs/hypermail/html-home/41-html/0221.html (last visited on May 20, 2003) (on file with author).

[90] CONFERENCE REPORT, *supra* note 88, at 3.

[91] *See* Groff, *supra* note 89.

cross-pollination rate dropped to 0.1 percent.[92] There was no cross-pollination in corn 1000 feet away. New biopharmaceutical regulations will require that farmers grow biopharm crops one mile, or 5,280 feet away from other crops.[93] Based on current data, it seems that the speculation over the risks of cross-pollination may be just that — speculation.

2. Cross-Contamination of Biopharmed Crops with Crops for Human Consumption

Another primary concern regarding farmers growing biopharmaceuticals in open-air fields is the potential that such biopharmed crops may contaminate food crops for human consumption. These fears were realized in November 2002, when the APHIS announced that ProdiGene, a Texas-based biotechnology company, had violated permit conditions under the Plant Protection Act.[94] Federal inspectors found permit violations at ProdiGene field test sites in Iowa in September 2002 and in Nebraska in October 2002.[95]

In the Iowa incident, a farmer planted soybeans after harvesting biopharmaceuticals in the same field.[96] However, stray cornstalks remained in the field.[97] Cross-pollination did not cause this accident.[98] Regardless, the USDA ordered ProdiGene to burn 155 acres of nearby food crops in case biopharm pollen drifted into the adjoining fields.[99]

The Nebraska episode was similar to that in Iowa. Prodigene conducted a field trial of biopharm corn genetically engineered to produce a

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92 *Id.*

93 Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11337, at 11338 (Mar. 10, 2003) (to be codified at 7 C.F.R. pt. 340).

94 *USDA Investigates Biotech Company For Possible Permit Violations, at* http://www.aphis.usda.gov/lpa/news/2002/11/prodigene.html (last visited March 4, 2004). Philip Cooper, *GM Crop Mishaps Unite Friends and Foes*, NEW SCIENTIST, Nov. 18, 2002 *available at* www.newscientist.com/news/news.jsp?idns99993073 (last visited Feb. 2, 2004).

95 *USDA Investigates Biotech Company*, *supra* note 93; Emma Hilt, *Scientists Scrutinize Biopharming*, The Scientist *at* http://www.biomedcentral.com/news/200303 21/04 (last visited (last visited Mar. 4, 2004). ProdiGene is a leading agricultural biotechnology company. *Compare Biopharmaceutical Contamination Could Be: Aids Vaccine or Blood Thickener, at* www.foe.org/new/releases/1102biopharml.html (last visited Mar. 4, 2004) (stating that review of USDA records show that ProdiGene has received eighty-five test permits for experimental open-air trials of genetically engineered biopharmaceuticals and chemical crops in at least ninety-six locations) *with* Philip Brasher, *Biotech Firm Under Fire, at* http://desmoinesregister.com/business/stories/c4789103/19755220.html (last visited Mar. 4, 2004) (asserting that ProdiGene has twenty-four test sites).

96 Stephanie Simon, *Fearing a Field of Genes*, L.A. TIMES, Dec. 23, 2002, at 1.

97 *Id.* at 1.

98 *Id.*

99 *Id.*

swine vaccine that protects piglets from diarrhea.[100] The corn was isolated from nearby crops, and surrounded by sterile crops acting as a buffer zone to catch any pollen.[101] In the fall, ProdiGene harvested the corn for testing.[102] That spring, the field was replanted with soybeans for human consumption. Under USDA regulations, ProdiGene inspected the field to ensure that there was no leftover biopharm crop that could potentially contaminate newly planted food crops. ProdiGene inspectors found no stray corn and discontinued inspections. USDA inspectors later found GM cornstalks in the soy crop. In violation of APHIS regulations, some of the GM corn had not been pulled, causing the biopharmed crops to be harvested along with the non-transgenic soy.[103]

These episodes illustrate some of the risks of growing crops in the natural environment. The biopharmed corn crop in Nebraska contaminated the soybeans because the tassled corn was not completely removed before the farmer harvested the soybeans.[104] Assisted by a hailstorm that loosened soil and spread seeds, corn from the pharmaceutical crop grew after the farmer sowed the field with soybeans.[105] The resultant 500 bushels of contaminated soybeans were delivered to a grain elevator and mixed with soybeans from other farms, thus adulterating a total of 500,000 bushels.[106] The USDA incinerated all 500,000 bushels, worth nearly $3 million.[107] While much of the debate has been over the potential for cross-pollination between biopharm plants and food crops, nota-

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100 *See* Simon, *supra* note 98, at 1. *But see Biopharmaceutical Contamination Could Be: Aids Vaccine or Blood Thickener*, *at* www.foe.org/new/releases/1102biopharml.html (last visited March 4, 2004), *supra* note 99 (observing that USA has refused to reveal what drug was grown in crop, and informing that research showed contaminants could be aids vaccine, blood-clotting agent, digestive enzyme, or industrial adhesive); *Legal Action Filed to Halt Planting of Biotech Crops Containing Pharmaceuticals*, *at* http://www.centerforfoodsafety.org/inthenews/bipharmrelease.htm (last visited Feb. 18, 2003) (announcing that GE Food Alert coalition filed formal petition with USDA calling for moratorium on planting of biopharm food crops, noting that USDA refused to identify biopharm contaminants or provide detailed account of biocontamination); *Prodigene Field Trials of Drug- and Chemical-Producing Corn*, *at* http://www.foe.camps/comm/safefood/biopharm/prodigenetrials.pdf (describing possible drugs grown in Prodigene biopharmed crops, including blood-clotting agent used to reduce blood loss during surgery, development of AIDS vaccine, digestive enzyme known as inhalant allergen, fungus-derived enzyme used for adhesives, experimental oral vaccines for hepatitis B, oral vaccine for pig gastrointestinal disease).

101 Simon, *supra* note 95, at 1.

102 *Id.*

103 Tom Zinnen, *Nebraska Crop Contamination Issue Briefing*, *at* www.biotech.wisc.edu/Education/prodigene.html (last visited Feb. 12, 2003).

104 *Id.*

105 *Editorial: Set Tough Rules for Biofarms*, DES MOINES REGISTER, Nov. 14, 2002, *at* www.DesMoinesRegister.com.

106 Simon, *supra* note 98, at 1.

107 *Id.*

bly, cross-pollination was not the cause of the Nebraska or Iowa incidents.

3. The Secrecy of Existing "Pharms"

As stated previously, 315 biopharmaceutical field site trials have been conducted in the United States in the last decade.[108] Information about the types of products companies are currently testing is very restricted, leading many interest groups to protest the lack of transparency involved with the biopharmaceutical permit process. There is a high degree of secrecy surrounding field test sites due to biotechnology companies' desire to keep their products and intellectual property confidential. Further, there is a desire to protect crops from anti-biotechnology activists who have destroyed fields with GM crops in the past.[109] Thus, the biopharm permit applicant almost always utilizes its "confidential business information" privilege, allowing the APHIS to refuse to divulge the source of the biopharmaceutical, the location of the field site, and the product grown at the field site.[110] Until these conflicts are resolved, "a veil of industry secrecy is necessary."[111]

III. CURRENT REGULATORY STRUCTURE

A. Regulatory Agencies in Charge of Oversight

Three federal agencies are responsible for the development, commercialization, and manufacture of biopharmaceuticals. These are the Occupational Safety and Health Administration (OSHA), the United States Department of Agriculture (USDA), and the Food and Drug Administration (FDA). OSHA regulates workplace safety, including people who work with biopharmaceuticals.[112] Under the Federal Food, Drug, and Cosmetic Act (FDCA),[113] the FDA regulates all human and animal drugs derived from bioengineered pharmaceutical plants intended for therapeutic, preventative, or diagnostic purposes. The FDA is responsible for clearing these products for human consumption. Because biopharming has yet to reach this stage, regulatory authority over the

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108 FREESE, *supra* note 12, at 9.

109 *See, e.g.*, Lee & Lau, *supra* note 85, at A1 (citing concerns of vandalism by anti-biotechnology activists, biotechnology company refuses to reveal location of planned biopharmaceutical).

110 FREESE, *supra* note 12, at 52.

111 Thomas P. Redick, *Biopharming, Biosafety, and Billion Dollar Debacles: Preventing Liability for Biotech Crops*, 8 DRAKE J. AGRIC. L. 115, 125 (2003).

112 BIOTECHNOLOGY INDUSTRY ORGANIZATION, REFERENCE DOCUMENT FOR CONFINEMENT AND DEVELOPMENT OF PLANT-MADE PHARMACEUTICALS IN THE UNITED STATES, 8 (2002), *available at* http://www.bio.org/pmp/PMPConfinementPaper.pdf (last visited Mar. 10, 2004).

113 21 U.S.C. § 351 (2001).

current phase of molecular farming falls primarily on the USDA's Animal and Plant Health Inspection Service (APHIS).

Under the Plant Protection Act,[114] the APHIS regulates biotechnology crops, including its importation, interstate movement, and release into the environment (inadvertently and through field testing). A biopharmaceutical producer must first obtain a permit from the APHIS before it can conduct field tests. Because the APHIS is in charge of granting permits and will do so prior to a manufacturer submitting a product application, the APHIS also addresses the National Environmental Policy Act's (NEPA) requirements.

NEPA requires federal agencies to consider the environmental impacts of their decisions, hence making environmental protection part of every federal agency's mandate. Under NEPA, agencies must prepare a detailed statement assessing any effects that a proposed action may have on the environment.[115] Therefore, the APHIS is required to respond to NEPA's dual concerns of improving decision-making by considering the long-term environmental consequences of federal actions, and to provide the public with that information. The APHIS should identify and evaluate possible environmental effects of field tests on a case-by-case basis, and prepare the necessary Environmental Assessments (EA) and/or Environmental Impact Statements (EIS).[116]

B. New USDA Regulations for Biopharming

In March 2003, the APHIS announced that it was strengthening the permit conditions for field tests of biopharmaceutical plants.[117] The APHIS Biotechnology Permitting Program is a flexible system, allowing the agency to alter its condition requirements in response to new information, public feedback, and technical innovation.[118] Field test permits include detailed conditions under which the permit is issued.[119] These permit conditions are aimed at establishing adequate confinement measures to ensure that there is no exposure of the biopharm crop to the

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114 7 U.S.C. § 7759(f) (2001).

115 National Environmental Policy Act of 1969 § 102(2)(C), 42 U.S.C. § 4331 (1994).

116 *Id.*

117 *USDA Strengthens 2003 Permit Conditions for Field Testing Genetically Engineered Plants, at* www.usda.gov/news/releases/2003/03/aphis030603.htm (last visited Jan. 23, 2003).

118 *See generally* Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11337 (Mar. 10, 2003) (to be codified at 7 C.F.R. pt. 340) (inviting public comment on proposed rules and advocating transparency in the regulatory process).

119 Introduction of Organisms and Products Altered or Produced Through Genetic Engineering Which are Plant Pests or Which There is Reason to Believe Are Plant Pests 7 C.F.R. § 340.0 (1997).

public, and very minimal exposure to the environment. All biopharm field test sites are also subject to inspection by the USDA[120] and the FDA.[121]

1. The Former Rules

The former rules required a twenty-five foot fallow zone around the field test site in order to prevent biopharm plants from mixing with food crops. Farmers were prohibited from growing the same crop for consumption on the biopharm field test site. The APHIS required that all farm equipment be adequately cleaned at the field site. If the biopharm crop was stored, it had to be maintained at a specific facility. Further, the regulations required each company to detail its production method and provide adequate instructions to its employees to ensure satisfactory production.[122]

The APHIS also had specific regulations for pharmaceutical corn. It prohibited farmers from growing any open-pollinated corn within a one-half mile radius of the field test site. Conventional corn within one-half mile to one mile of the field test site had to be planted at least twenty-one days before or after the pharmaceutical corn was planted. The APHIS enacted these measures to confine corn pollen so that biopharm corn could not pollinate surrounding corn. Companies could also utilize detassling and bagging measures to control pollen flow.[123] When using these methods to control pollen flow, all corn within one-quarter mile had to be temporally isolated from the regulated corn by twenty days. The APHIS also required such corn to be bagged or detassled. Border rows of plants serving as buffer strips between biopharm corn and non-transgenic corn could be used to reduce the isolation distance requirements. These barrier crops reduce the chances of cross-pollination by increasing the distance pollen has to travel to conventional food crops. They also serve as a barrier to insects.[124]

The permit conditions also included compliance measures. The APHIS had a target goal of inspecting all biopharm field test sites at least once a year. Further, APHIS required field data reports for all field tests, documenting any adverse effects of the regulated plants, such as

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120 *Id.* § 340.9; Animals and Animal Products, 9 C.F.R. § 101-108 (2004).

121 42 U.S.C. § 262 (2001); 21 U.S.C. § 374 (2001).

122 *See Highlights of the Federal Register Notice: Changes in the Permit Conditions for 2003*, *at* http://www.aphis.usda.gov/ppd/rad/webrepor/brs.html.

123 PHARMING THE FIELD, *supra* note 13, at 14. Bagging simply involves placing bags around the corn tassels to catch the pollen. *Id.* Detassling the corn requires removing the portion of the plant that stores most of the pollen. *Id.*

124 *Id.*

unusual occurrences, effects on other plants, non-target organisms, and the environment.[125]

2. The Proposed Changes

For the most part, the APHIS is proposing changes that will strengthen the permit requirements for biopharm plants. However, the APHIS is relaxing its complete ban on growing the same crops for consumption on the biopharm crop field site. Instead, production of food or feed crops on the field test site and in the fallow zone will now merely be restricted.[126]

With this exception, the remaining changes increase the stringency of the permit conditions. For example, the APHIS is expanding the fallow zone's minimum separation distance between crops from twenty-five feet to fifty feet.[127] It is also requiring that certain farm equipment, such as planters, be dedicated solely for use in farming pharmaceutical crops. Cleaning such equipment before use with food crops will no longer suffice under the new permit regulations.[128] Other farm equipment not falling under this requirement, such as tractors, will still need to be maintained and cleaned under the old standard. The new regulations mandate that biopharmaceuticals and farm equipment both be stored in dedicated facilities reserved only for such use.[129] The APHIS is expanding the protocols required from each company to include specified procedures for seed cleaning and drying, which the APHIS must approve prior to granting the permit. Furthermore, each company must imple-

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125 Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11337 (Mar. 10, 2003) (to be codified at 7 C.F.R. pt. 340).

126 *See* Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11337 (Mar. 10, 2003) (to be codified at 7 C.F.R. pt. 340); *see also Highlights of the Federal Register Notice*, *supra* note 121 (listing permit changes, including allowing non-transgenic food crops to be grown in the fallow zone).

127 *See* Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11337, at 11338 (Mar. 10, 2003) (to be codified at 7 C.F.R. pt. 340); *see also Highlights of the Federal Register Notice*, *supra* note 121 (noting expansion of separation zone).

128 *See* Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11337, at 11338 (Mar. 10, 2003) (to be codified at 7 C.F.R. pt. 340); *see also Highlights of the Federal Register Notice*, *supra* note 121 (describing rule that tools used for biopharm plants be dedicated solely to use harvesting such crops).

129 *See* Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11337, at 11338 (Mar. 10, 2003) (to be codified at 7 C.F.R. pt. 340); *see also Highlights of the Federal Register Notice*, *supra* note 121 (describing rule that tools used for biopharm plants be dedicated solely to use harvesting such crops).

ment a training program for its employees, approved by the APHIS, to ensure compliance with the new standards.[130]

The APHIS has also strengthened its field test conditions for pharmaceutical corn. The isolation distance between food crop and open-pollinated corn has been doubled to one mile. This is eight times greater than the minimum distance of 680 feet required to protect hybrids from cross-pollination.[131] The temporal isolation period for corn to be grown around controlled-pollinated biopharm corn has been increased to twenty-eight days.[132] In addition, the APHIS will no longer allow border rows to reduce the isolation distance between corn crops. Eliminating these border crops will reduce the amount of plant material requiring disposal after the field tests are complete. The APHIS also hopes to lessen the chance of biopharm plants being inadvertently mixed with non-transgenic plants. However, by removing the incentive to use barrier rows, the APHIS has decreased the likelihood of companies utilizing these barriers, thus reducing some of the potential benefits such measures provide.[133]

The APHIS has also strengthened its compliance measures. Specifically, the APHIS is increasing the number of field site inspections. An APHIS agent will inspect a field test site at least once, and the APHIS hopes to arrange more inspections with each site's production schedule. Under the new regulations, field data reports must document additional issues, such as the planting dates of biopharm crops, the planting dates of adjacent food or non-transgenic crops, and the assessments of detassling efforts. By increasing the depth of the field reports, the APHIS expects to better monitor the field tests and identify potential problems.[134]

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130 *See* Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11337 (Mar. 10, 2003) (to be codified at 7 C.F.R. pt. 340).

131 *See* Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11337, at 11338 (Mar. 10, 2003) (to be codified at 7 C.F.R. pt. 340); *see also Highlights of the Federal Register Notice*, *supra* note 121 (stating requirement increase of isolation distance between non-transgenic crops and biopharm crops).

132 *See* Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11337, at 11338 (Mar. 10, 2003) (to be codified at 7 C.F.R. pt. 340); *see also Highlights of the Federal Register Notice*, *supra* note 121 (noting that non-transgenic corn must be isolated for 28 days before or after regulated corn is planted).

133 *See generally* Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11337 (Mar. 10, 2003) (to be codified at 7 C.F.R. pt. 340) (relaxing requirement that farmers use barrier rows between G.M. crops and non-transgenic food crops).

134 *See* Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11337, at 11339 (Mar. 10, 2003) (to be codified at 7 C.F.R. pt. 340); *see generally Highlights of the Federal Register Notice*, *supra* note 121

The new permit conditions will apply to the 2003 growing season. The proposed changes published in the Federal Register also encouraged public commentary on the new permit requirements as well as various biotechnology issues. As part of its effort to increase the transparency of its regulatory approach, the APHIS sought suggestions on additional measures that would make information more readily available to the public. It also encouraged commentary on alternative procedures to guarantee the adequacy of field confinement measures and the scientific rationale on which such suggestions are based. Furthermore, the agency sought ideas on the best methods for ensuring compliance with permit conditions, such as increased agency monitors and third-party auditors.[135]

IV. Analysis of the Biopharming Regulations

Studies thus far demonstrate that there are, at most, minor risks of cross-pollination. This, coupled with incidents such as the volunteer crops accidentally grown in the Nebraska field trial, indicate that the legislative focus should be on regulations that guarantee efficient harvesting and removal of biopharm crops. The APHIS apparently recognizes this in its new proposals, calling for increased regulatory oversight and on-site inspections. However, it is imperative that the APHIS make these oversight measures mandatory and legally enforceable, rather than the discretionary field site visits mandated by its former regulations.

A key flaw of the current system is that, while NEPA requires that a federal agency prepare a formal Environmental Assessment (EA) or Environmental Impact Statement (EIS) prior to approving a biopharm field, the APHIS rarely requires one. The USDA has made an exception for agency actions involving field trials in which containment procedures must be approved.[136] The current regulations do require a more detailed assessment of a company's containment measures. However, there is not enough overlap to justify disregarding NEPA's EA/EIS requirements. To date, while hundreds of permits have been issued for biopharmaceutical crops, the APHIS has yet to conduct a single EA or EIS to determine the potential environmental or health risks associated with these permits.[137] The EA/EIS process would force companies to extensively evalu-

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(inviting public comment and additional proposals to improve field test confinement and future regulations of GM crops).

135 *See* Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11337, at 11339 (Mar. 10, 2003) (to be codified at 7 C.F.R. pt. 340); *see generally Highlights of the Federal Register Notice*, *supra* note 121 (inviting public comment and additional proposals to improve field test confinement and future regulations of GM crops).

136 Pharming the Field, *supra* note 13, at 4.

137 *See* Gregory A. Jaffe, *Plants as Factories for Pharmaceutical and Industrial Products*, SJ033 A.L.I. - A.B.A. 191, 194-95 (2003).

ate the sufficiency of their containment measures because they would have to consider the consequences if their containment procedures failed.

The National Research Council (NRC), the principal operating agency of National Academy of Sciences, have both voiced concerns about the agency's apparent disregard of NEPA's requirements.[138] The National Academy of Science issued a report urging the APHIS to more rigorously review the potential environmental effects of biopharm crops.[139] Similarly, a recent NRC report determined that environmental risks posed by biopharmaceutical plants cannot be predicted and thus should be assessed on a case-by-case basis.[140] However, because the current regulatory measures do not require such an evaluation, and the APHIS is not enforcing NEPA's EA/EIS mandate, to date no biopharm crops have been thoroughly evaluated for environmental risks.

But how effective can the law and legal remedies be in this area? Potentially, the law could efficiently implement preventative measures. Such regulations should decrease the risks involved in biopharming in a cost-effective manner without suppressing potential growth in the industry. In many respects, the APHIS regulations are able to balance the risks while allowing biopharm field testing to continue. For example, they are very cautious in its regulation of corn crops by requiring a substantial distance between biopharm corn and conventional corn.

On the other hand, the law is addressing a field in which it may not be very effective. No law is going to prevent wind from carrying pollen through the air. Legal remedies tend to wait until injury occurs. But in a worst-case scenario of inadvertent contamination of food crops and accidental human consumption of food tainted with biopharmaceuticals, it would then be too late. Money would not compensate the victims, and an injunction would be incapable of stopping or preventing further harm. Further, there are some aspects of biopharming that should be more stringently regulated. For example, the APHIS should require border rows to serve as an extra preventative barrier to wind pollination. If the APHIS does not implement equivalent measures in the future, then biotechnology companies should self-impose such production control policies. Numerous lawsuits filed after the StarLink corn debacle illustrate that consumers and farmers alike will accuse biotechnology companies of negligence in the event of an accident. It may prove beneficial and be more cost-effective and efficient to implement preventative protocols

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138 *See* Jaffe, *supra* note 131; Redick, *supra* note 110, at 124; *see also The National Research Council, at* http://www.nas.edu/nrc/ (last visited Apr. 24, 2004) (describing role of National Research Council as principal agency within National Academy of Sciences).

139 *See* Redick, *supra* note 113, at 124-25.

140 *See* Jaffe, *supra* note 131.

early on rather than be forced to employ remedial measures after an incident of food contamination or other mishap.[141]

Regardless of whether a biotechnology company grows biopharmaceutical plants itself or hires an independent farmer to do so, the responsibility for production controls belongs to the company.[142] The biotechnology industry has a strong interest in ensuring that there is zero contamination of non-transgenic food crops with biopharmaceuticals. The public backlash as a result of inadvertent mixings, especially those with the potential to enter the food supply, would be detrimental to biopharmaceutical producers. Without buyers for biopharmaceuticals, there would be no market. Therefore, biotechnology companies should implement measures that decrease the likelihood of inadvertent mixing of pharmaceutical plants with food or feed crops. Companies could adopt methods that allow the bioengineered pharmaceutical plant to be easily distinguishable from its food counterpart. For example, industry could genetically alter the physical appearance of the plant by using a different color or leaf pattern. Companies could experiment with various physical barriers to decrease pollen flow, keep out intruders, and exclude wildlife from the field site.

Notably, the APHIS does not require any of these measures. But is it necessary for the APHIS to require them? As demonstrated by the public backlash over GM crops after cross-contamination incidents, the biotechnology industry has a huge incentive to efficiently police and regulate itself.

CONCLUSION

While there are risks involved with growing biopharmaceuticals in outdoor fields, these risks do not justify such extreme measures as banning biopharming, requiring indoor cultivation, or prohibiting companies from using food crops with which they are familiar. The possible advantages of farming biopharmaceuticals should be weighed against the hazards. Current biotechnology practices of using cell cultures and indoor laboratories to produce pharmaceuticals simply cannot meet demand due to monetary costs and production limitations. Biopharming presents an innovative way to produce necessary medication in a cost-

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141 *See, e.g.*, Bill Hord, *Back in Good Graces StarLink Corn Appears to Have BeenIsolated and Contained, Restoring Confidence in Foreign Markets*, OMAHA WORLD-HERALD COMPANY, Oct. 20, 2002, at 1d (documenting aftermath of StarLink corn debacle, including numerous class action lawsuits, and $9 million settlement of one case, in which plaintiffs filed suit against several food companies for allowing StarLink to get into their food); David Barboza, N.Y. TIMES, *Negligence Suit Is Filed Over Altered Corn*, Dec. 4, 2000, at C2. (describing class action lawsuit filed against StarLink corn developers, accusing them of harming farmers through negligence).

142 21 C.F.R. § 200.10, parts 210, 211, 514.1, and 820.50.

effective manner, thereby potentially decreasing the cost of drugs while increasing their availability. In many cases, it will cost significantly less to grow plants to supply medication because plant-based techniques do not require the same expensive capital investments.[143]

Furthermore, the additional potential benefits of biopharmaceuticals can make this next wave of biotechnology revolutionary in the effects it may have on the methods by which medication is produced, and its cost, form, and availability to the public. Conceivably, any therapeutic protein can be mass-produced in crops.[144] Important and life-saving medication, with functions ranging from treating AIDS, breast cancer, arthritis, and the flu, can potentially be produced by growing them in affordable quantities in corn or tobacco.[145] Through molecular farming, production of pharmaceuticals could also be more easily increased if demand for the medication increases. There is enormous promise in the future of biopharmaceuticals, and while there are risks involved, there are always uncertainties entailed with the development of any medication.[146] Of course, molecular farming will also result in resistance from those opposed to GM crops in general. However, this also serves an important function by acting as an additional check on biotechnology companies field testing biopharmaceuticals.

Ultimately, regulations should impose strict preventative and confinement protocols without stifling innovation and development. At this stage, the potential benefits of biopharming outweigh the potential risks. Personally, the possibility of not experiencing shortages of vaccines during the next flu season, and having the option of eating my flu vaccine rather than injecting it are both encouraging alternatives. This, as an example of the potential benefits of biopharmaceuticals, provides enough incentive to allow biotechnology companies to continue their field testing, with strict regulations from both government agencies and the biotechnology companies themselves.

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143 *Advantages of Plants to Produce Therapeutic Proteins*, *at* http://www.bio.org/pmp/factsheet3.asp (last visited Apr. 24, 2004).

144 Dr. William O. Robertson, *Protein-based therapeutics today's penicillin*, SEATTLE POST-INTELLIGENCER, *available at* http://seattlepi.nwsource.com/opinion/133759_protein06.html (last visited Apr. 24, 2004).

145 *See, e.g., id.* (imagining affordable harvesting of enough anti-arthritic globulin for whole world from less than fifty acres of corn).

146 *See also id.* (noting that risks seem minuscule when compared to other risks with development of medication, giving example of administering painful penicillin shots in its early stages, when it had not been adjusted for pH or osmolarity).