Bio-Pharming in Colorado:
A Guide to Issues for Making Informed Choices

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Full Report

Produced by:

Colorado Institute of Public Policy

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Knowledge to Go Places

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Executive summary

Making informed decisions about bio-pharming in Colorado comes down to case-by-case analysis of **economic-development benefits** and **health, environmental and market-related risks**.

Raising genetically engineered crops for pharmaceuticals and industrial compounds often is called "molecular farming" or "bio-pharming." Scientists have envisioned the technology for 20 years, but application is in its infancy. In summer 2004, the first bio-pharm crop was planted in Colorado. The experimental research crop of 2,000 engineered corn plants puts Colorado at a policy crossroads:

1. Can bio-pharming bring long-term economic and other benefits to Colorado and its rural areas, and to what extent?
2. Does the technology present unacceptable health, environmental or market-related risks?
3. Will the technology add economic value to Colorado's agricultural sector or pose a threat to its existing markets?
4. What are the conditions under which Colorado can maximize benefits and minimize risks of bio-pharming?
5. Which communities are best suited for this new technology?
6. Should the state or its communities pursue bio-pharming?

This paper addresses these important questions by providing relevant scientific information and frameworks to guide decision-making.

Key findings

- **Economic development:** Bio-pharming may offer a new way for Colorado to capitalize on climactic, geographical and agricultural assets to boost rural economies and the state economy. This could be the technology's chief benefit for Colorado. Such economic development most likely would occur if Colorado attracts and integrates several aspects of bio-pharming industry – not only crop cultivation, but processing operations and research and development.
- **Potential risks:** Possible risks of bio-pharming include human-health, environmental and market-related problems that could arise from inadvertent bio-pharm gene flow or accidental commingling. Market-related risks, a particular concern among Colorado residents, include possible negative impacts of bio-pharming on existing crop markets and associated legal liabilities. Such market risks can arise from perception alone, regardless of any actual danger posed by bio-pharming.
- **Reliable information:** Participants in bio-pharming focus groups held in four agricultural communities in Colorado were concerned about the availability of reliable bio-pharming information for state residents and decision makers. Reliable information is central to understanding potential benefits and risks, and likewise is central to sound decision-making.

These findings suggest that decisions about bio-pharming should rely neither on hope nor on fear. Policy decision frameworks, grounded in science and mindful of community values, are offered to help decision makers systematically assess the potential benefits and risks of bio-pharming. The frameworks are based upon the following principles:

Decision-making framework principles

- **Case-by-case analysis:** Science and community focus groups concur that case-by-case assessment is needed to understand both benefits and risks. Each bio-pharm proposal would undergo analysis to determine its potential for community economic development and its potential for posing health, environmental and market-related risks. Such examination, illustrated in charts in this paper, draws upon relevant data, including scientific findings. For example, case-by-case benefit assessments account for variables including a bio-pharm developer's required infrastructure and employment needs; risk assessments account for important variables in crops, genetically engineered traits and growing environments.
- **Stakeholder involvement:** Science and community focus groups suggest that sound decisions arise from stakeholder involvement in bio-pharming policy formation in Colorado. State residents who are interested in and potentially affected by bio-pharming are positioned to understand the significance of established benefits and risks and can articulate the needs and values of their communities.
- **Relevant issues:** A focus on relevant issues guides informed and well-reasoned policy decisions. Science-based knowledge and a clear understanding of community values clarify the relevant bio-pharming issues in Colorado and its communities. Such a focus could drive regulations and economic-development strategies to help the state and its communities maximize benefits and minimize risks from bio-pharming.

These findings and decision framework principles provide a systematic, reasoned and fact-based approach to making informed choices about bio-pharming in Colorado.

Introduction

Agriculture is entering a new era – an era when genetically engineered crops are grown not only for human and livestock food, but also to produce medicine and industrial chemicals. Raising crops for plant-made pharmaceuticals and industrial compounds, which scientists have envisioned for some 20 years, often is called "molecular farming" or "bio-pharming."

This emerging form of agricultural biotechnology is part of a modern revolution in genetics, and applications that could serve human health and economic development are becoming increasingly clear. Bio-pharming could yield more and cheaper medication for people plagued by a range of illnesses, helping to treat widespread health problems. It could present new economic opportunities for some growers, for companies involved with drug development and production, and for states and communities where associated activities are based (Dry, 2002).

Corn, soybeans, rice and tobacco can be used as biological factories to produce pharmaceuticals that help prevent or treat ailments including heart disease, cancer, arthritis, Alzheimer's disease, human immunodeficiency virus and diabetes (Rogers, 2003). Likewise, engineered plants can be sources of industrial products now derived from nonrenewable resources, including industrial oils, detergents, gasoline substitutes, biodegradable plastics and rubber compounds (University of California, 2001).

Bio-pharm crops are engineered to contain genes from mammals, microorganisms or other plants, resulting in modifications that do not naturally occur. The crops are meant only as factories to produce specialized proteins for drugs and industrial products. Bio-pharm crops are not intended to replicate themselves in farm fields or to mingle in the natural environment; they are not intended as food for humans, livestock or wildlife. For these reasons, the cultivation of bio-pharm crops has sparked controversy and presents regulatory agencies and others with the challenge of ensuring that novel genes and plant material are controlled and do not present unacceptable risk to people, animals, the environment and markets for other crops ("Drugs in crops," 2004; Flinn and Zavon, 2004; Center for Science, 2002).

Indeed, safety, defined broadly, was the top bio-pharming issue identified during four focus groups held by the Colorado Institute of Public Policy in May 2004. The bio-pharming discussions, in an agricultural community in each quadrant of the state, involved 56 stakeholders, including conventional farmers, organic farmers, agricultural businesspeople, economic-development experts, cooperative extension agents, county commissioners, and members of interest and industry groups (See "Colorado stakeholders: insights, ideas and opinions" section and Appendix A for summaries). Many meeting participants agreed that bio-pharming presents potential economic benefits for Colorado and its citizens. They also agreed that plant material must be kept out of the human food supply, and that unintended effects of bio-pharming on the environment and existing agricultural markets must be avoided if the technology is to move ahead and communities are to gain.

This paper explains bio-pharming and its genesis. It offers, from a research perspective, frameworks to help decision makers in Colorado and its communities determine whether to pursue bio-pharming, and how to do so in ways that could yield the greatest benefits with fewest risks.

The Colorado context

Bio-pharming already has been introduced on Colorado's northeastern plains. The state's first bio-pharm crop – about 2,000 genetically engineered corn plants – was sown on a 90-foot-by-35-foot plot in Logan County in spring 2004.[1] An Iowa State University researcher received a federal permit, which the Colorado Department of Agriculture endorsed, to grow the bio-pharm crop to develop a corn-based edible vaccine system for livestock. The seeds were modified with a component from the E. coli bacterium; the bacterium causes a diarrheal disease widely known as "traveler's disease." The bio-pharm corn was engineered to replicate the bacterium component, a protein that by itself does not cause disease. The protein manufactured in bio-pharm corn seeds is being used in Iowa State research for vaccine development; studies eventually could lead to a new product that boosts the effectiveness of human and animal vaccines against a range of illnesses, and to a human vaccine against diarrhea that often is fatal in developing countries.[2]

Bio-pharming emerged even earlier in Colorado. In spring 2003, the U.S. Department of Agriculture granted a permit to Meristem Therapeutics of Clermont-Ferrand, France, which was subsequently endorsed by the Colorado Department of Agriculture.[3] The biotech company was permitted to grow 30 acres of bio-pharm corn near Holyoke in Phillips County on the state's northeastern plains. The corn was designed to produce a therapeutic protein, an enzyme called lipase, to treat digestive problems in patients with cystic fibrosis (Mison, 2004). Meristem put its plans on hold in 2003 because federal and state approval came too late in the season to grow and harvest a crop (Auge, 2003a, 2003b; Becker, 2003; "French company gets OK," 2003). Meristem's bio-pharm permit for Colorado expired in June 2004, and the company must re-submit an application to regulators if it wants to pursue bio-pharming in the state.[4]

These are but two examples of how bio-pharming might be conducted in Colorado, and other proposals could be in the offing as bio-pharming expands. This suggests that Colorado is at a crossroads: It may accept a passive role in bio-pharming, evaluating proposals on a piecemeal basis, or it may take a proactive role with the technology, developing policies to responsibly and profitably adopt bio-pharming in a manner consistent with the values and standards of state residents (European Commission, 2002). If Colorado pursues the latter approach, the state's assets could prove attractive to bio-pharming companies.

- The state presents **relative ease in assuring isolation** for open-air bio-pharm crops, such as corn (See Appendix B for crop information). That is significant as regulators, growers and biotech companies seek to prevent pollen and other plant materials from mingling with wild and cultivated plant species. Confining bio-pharm plant material is critical to minimizing risks to the environment, food supplies and agricultural markets (Biotechnology Industry Organization, 2004). Further, the crop isolation possible in Colorado contrasts with that available in parts of the Midwest, where bio-pharming has gained a foothold in Corn Belt states including Nebraska and Iowa.
- The state presents **potentially favorable growing conditions** for bio-pharming. They include the possibility of high crop yields from irrigated fields; comparatively few problems with insects and disease; and the sunny days and moderate temperatures important for crop production. These advantages are tempered by a short growing season in some parts of the state.

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[1] From U.S. Department of Agriculture Biotechnology, Biologics and Environmental Protection Application for Permit, filed by Dr. Kan Wang, Department of Agronomy, Iowa State University, May 5, 2004; and Post-Planting Report for permit number 04-131-01R, filed with Colorado Department of Agriculture July 1, 2004.

[2] Personal communication, Dr. Kan Wang, director, Iowa State University Center for Plant Transformation, and associate professor, Agronomy Department, July 9, 2004.

[3] Information about Meristem Therapeutics' plant-made pharmaceutical program is available at: www.meristem-therapeutics.com/GB/intro.htm.

[4] Personal communication, Jim Miller, director of policy and communications, Colorado Department of Agriculture, July 7, 2004.

- Colorado also has **261 greenhouse farms** with 19.90 million square feet of capacity, some of which might be used for bio-pharm crops suited to enclosed environments.[5] This total capacity suggests Colorado might have a comparative advantage attracting companies pursuing greenhouse bio-pharming, and that such firms may help increase returns to greenhouses requiring high capital investment.
- Colorado's **agricultural heritage** presents a tradition of farming know-how and success, placing agriculture among the top industries in the state (Cornelius, 2002). The state has a demonstrated ability to grow some of the main crops used in early bio-pharming trials, and likely has the ability to successfully grow others.
- Colorado has a **thriving scientific community**, an infrastructure of training and research facilities, and a vibrant biotech business community, which offer potential research partnerships.

Why bio-pharming

Many human ailments can be traced to the body's failure to make a specific protein or to make it appropriately. Solving this problem is difficult: Most protein-based drugs cannot be synthesized and must come from a living source. Their manufacture typically occurs in sterile fermentation facilities, where genetically engineered microorganisms or mammalian cells are cultured to produce medicinal proteins in stainless-steel tanks, called bioreactors (Felsot, 2002). This method has produced a number of protein-based therapies for treatment of diabetes, cancer, renal failure and genetic clotting disorders, among other conditions (Walsh, 2000).

But drug-fermentation facilities have huge capital construction costs – an estimated $500 million each – and take as long as seven years to build. As a result, the biotechnology industry has been unable to keep up with mushrooming demand for some medication (Associated Press, 2002; Roosevelt, 2003). For example, the biotech company Amgen reportedly has been unable to meet demand for Enbrel, a protein-based arthritis medicine made in mammalian cell cultures (Alper, 2003).

Another method for obtaining biopharmaceuticals is to extract them from animal and human tissues. Insulin, for instance, is derived from pig and cow pancreas, and blood proteins come from human blood (Freese, 2002). But these are high-cost procedures that carry risk of transmitting infectious disease. And current methods for mass production of medicinal proteins are not sufficient to meet all potential needs (Huang, 2000; Walsh, 2000).

For these reasons, scientists are exploring how plants might be used as drug factories. With advances in genetic engineering over the past two decades, plants, called "the most efficient producers of proteins on earth," can be modified to produce a wide range of highly complex proteins (Biotechnology Industry Organization, 2002). The proteins can be extracted, purified and used as pharmaceuticals, potentially resulting in cheaper and more readily available therapeutic products.

Medicinal proteins produced in plant seeds also are touted as highly stable and easily stored. This is important for pharmaceutical delivery to regions with little refrigeration, such as developing nations (Pew Initiative on Food and Biotechnology, 2002b).

Studies show that genetically engineered plants can produce medicinal proteins about 80 percent cheaper than fermentation systems and could reduce the costs of goods by as much as 50 percent (Mison and Curling, 2000; Biotechnology Industry Organization, 2002; Crosby, 2003).[6] For example,

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[5] The 2002 USDA Census for Agriculture, the most recent, defines a greenhouse farm as one that operates under cover; the total capacity listed includes glass greenhouses, cold frames, cloth houses and lath houses. The 2002 report is at http://www.nass.usda.gov/census/. Definitions are at http://www.nass.usda.gov/census/census02/volume1/co/co2appxa.pdf, pp. A-11 and A-18.

[6] Crosby reports that the cost of producing drugs could drop from $50 to $100 per gram using fermentation systems to $12 to $15 per gram using transgenic crops; Mison and Curling report that the cost would drop from $50 to $100 per gram using yeast cultures to $13 to $14 per gram using transgenic plants.

antibodies that cost thousands of dollars per gram might be produced in plants for $200 per gram (Ohlrogge and Chrispeels, 2003). In addition, biotech companies might be able to quickly respond to rising demand for treatments by planting more bio-pharm acreage (Pew Initiative on Food and Biotechnology, 2002b).

Scientific knowledge has greatly expanded in molecular biology and genetics, opening the door to bio-pharming (Rogers, 2003). Partly through mapping of the human genome, researchers have gained new understanding about genes associated with human diseases, which helps suggest treatments. The federally funded U.S. Human Genome Project,[7] which was completed in 2003 and was a major catalyst for the biotechnology industry, provided up to 10,000 possible molecular targets for protein pharmaceuticals (Walsh, 2000). These proteins could be used in the treatment and prevention of cancer, heart disease, inflammatory diseases, respiratory disorders, genetic conditions and infectious diseases. In some cases, plant-made pharmaceuticals might even be tailored to a patient's unique genetic makeup.

Scientists also have worked to perfect genetic-engineering techniques so a corn plant, for instance, can be directed to replicate a therapeutic protein in only its seeds, and a potato plant can be directed to replicate a medicinal protein in only its tubers. This provides controls over novel genetic material.

With such advances, biotech companies are developing an estimated 500 medicinal proteins worldwide, most in the United States (Walsh, 2000). The subcategory of interest in this paper – the number of plant-made pharmaceutical proteins under development – is currently smaller. U.S. Department of Agriculture records show that from 1991 to 2004, federal officials authorized about 230 open-air field trials of crops engineered to produce antibodies, pharmaceutical proteins, industrial enzymes and other novel proteins in 36 states and Puerto Rico.[8] The crops most often used in these trials include corn, tobacco, soybeans and rice, with corn used most frequently by far. Recent records show that bio-pharm developers planted nine test plots, including one in Colorado, after receiving USDA approval during 2003-04 (APHIS, 2004b). Bio-pharm crops most recently planted were genetically engineered corn, tobacco, safflower and rice; the nine plantings covered just 44 acres nationwide.

None of the plant-made pharmaceuticals under development has been fully commercialized. At this point, all bio-pharming activities are in the form of research and testing; thus, comprehensive assessment of the safety and effectiveness of plant-made pharmaceuticals is lacking. But pharmaceuticals from plants may reach the market in the latter half of this decade (Ohlrogge and Chrispeels, 2003).

Some drug companies foresee a large future market for plant-made pharmaceuticals.[9] These companies have a vested interest in bio-pharming's future, and the market's ability to grow significantly depends on whether biotech companies can profitably make safe and effective bio-pharm products. Only continued research will answer those crucial questions.

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[7] Information about the U.S. Human Genome Project, coordinated by the U.S. Department of Energy and the National Institutes of Health, is at http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml.

[8] Virginia Tech University maintains the U.S. Department of Agriculture database of publicly available information regarding biotechnology field-trial permit applications at its Information Systems for Biotechnology website, www.nbiap.vt.edu/cfdocs/fieldtests1.cfm. Search on Phenotype: antibody (30 approved applications), industrial enzyme(s) (18 approved applications), novel protein (98 approved applications) and pharmaceutical protein (84 approved applications) for the crops considered in this report.

[9] Dr. Guy Cardineau, a Dow AgroSciences molecular and cellular biologist, discussed market projections during the Plant-Derived Biologics Seminar organized by the federal Food and Drug Administration and the federal Animal and Plant Health Inspection Service, April 5, 2000, at Iowa State University. He said that the potential market for all products that can be made in plants, called "output traits," could grow to $200 billion by 2010 (bio-pharm products would make up one category of those output traits). Many experts think such projections are overly optimistic. Proceedings available: www.fda.gov/cber/minutes/plnt1040500.pdf.

Other companies have signaled uncertainty for bio-pharming's short-term feasibility: Monsanto, the world's leading agricultural biotechnology company, announced in October 2003 that it would discontinue its plant-made pharmaceuticals program in favor of more immediately profitable businesses (Pollack, 2003; Suhr, 2003). CropTech Corp., a biotech company well-known in the industry for research into production of therapeutic proteins in tobacco, filed for bankruptcy protection in March 2003, even after attracting $2.3 million in venture capital, a $2 million loan from the state of Virginia, and the involvement of tobacco farmers seeking alternate markets (Dellinger, 2003; Stewart, 2003).

Despite uncertainties, a number of biotech firms are actively pursuing plant-made pharmaceutical technology. They include: Biolex, Ceres, Chlorogen, Dow AgroSciences, Epicyte, Large Scale Biology Corp., Medicago, Meristem Therapeutics, Planet Biotechnology, ProdiGene, SemBioSys Genetics, Syngenta, and Ventria Bioscience (Biotechnology Industry Organization, 2002). For instance, Meristem is conducting clinical trials with lipase produced in corn for treatment of cystic fibrosis; Large Scale Biology likewise is in clinical trials with vaccine produced in tobacco plants for treatment of non-Hodgkin's lymphoma; Epicyte will soon begin clinical trials with medical proteins grown in corn and rice to treat herpes; and Large Scale Biology and Planet Biotechnology are conducting clinical tests with an antibody produced in tobacco to treat dental caries (Biotechnology Industry Organization, 2002; Large Scale Biology, 2004a).

Scientific networks and universities also are conducting research with plant-made pharmaceuticals. One recent example: A consortium of scientists representing 11 European countries and South Africa received the equivalent of about $14.5 million from the European Union to develop bio-pharm vaccines and other treatments for major worldwide diseases such as AIDS, rabies, diabetes and tuberculosis. The consortium, called Pharma-Planta, aims to have greenhouse-grown bio-pharm products in clinical trials by 2009. The project is significant in part because Europe generally has been opposed to all genetically engineered plants (Elliot, 2004; Probert, 2004).

Bio-pharming science and its implications

Bio-pharming is an outgrowth of plant genetic engineering. The technology begins with DNA, or deoxyribonucleic acid, molecules that are shaped as double helixes and are present in the cells of all living organisms. DNA stores an organism's genetic information and orchestrates the metabolic processes of life (Polancic, 2003).

Each double-stranded DNA molecule contains many genes, the basic physical and functional units of heredity that together help direct trait development (The "genome" is an organism's complete set of genetic material). A gene, as a segment of DNA, carries coding for constructing proteins. Proteins, in turn, provide structures for cells and tissues and function as enzymes to catalyze essential biochemical reactions.

Figure 1: Making a modified protein

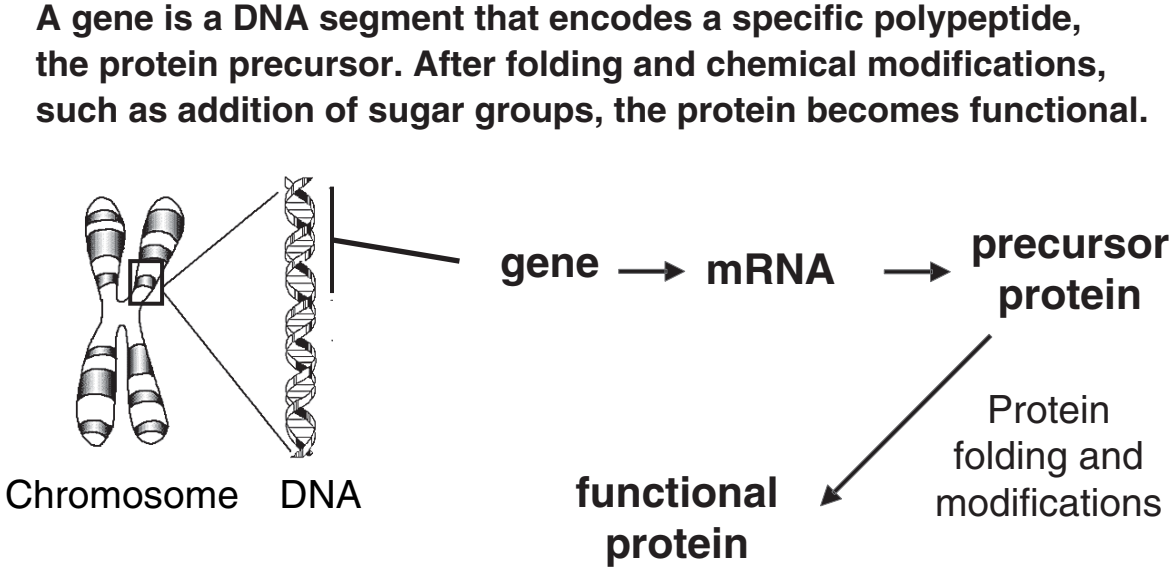
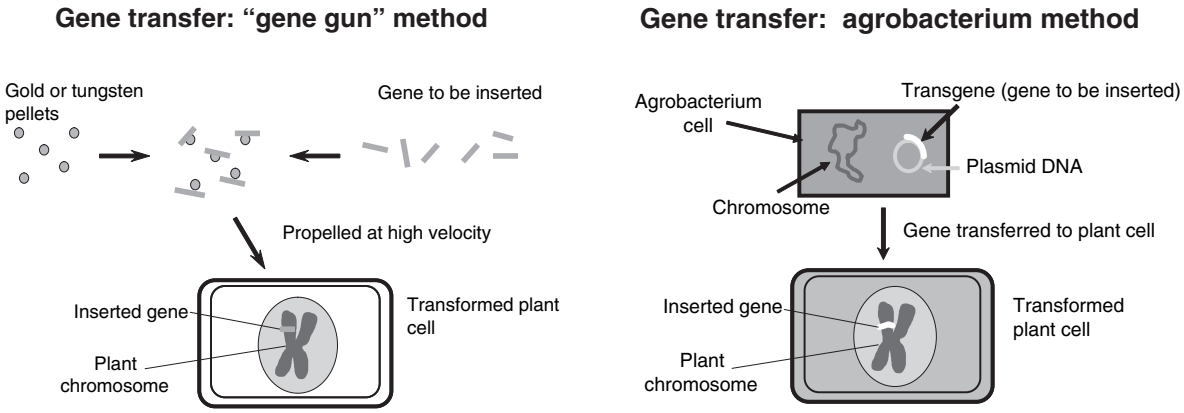


Figure 2: Two methods of gene transfer



Some of bio-pharming's scientific challenges are to identify proteins that might help solve health problems; to manipulate genes so that proteins of interest might be produced in high volumes in plants; and to perfect techniques so that pharmaceutical proteins might be extracted from plants and purified for safe and effective medicinal use.

In bio-pharming, genes are taken from mammals, microorganisms or other plants; they are amplified, modified and inserted into plants to replicate (See Figure 1). The technology that allows introduction of new genes into plants is more than 20 years old (Fraley et al., 1985). Genetically engineered organisms, including bio-pharm crops, often are referred to as "transgenic" because they contain gene sequences, known as "transgenes," that have been artificially inserted from the same or a completely different species (See Figure 2).

Techniques in genetic engineering often are called "recombinant DNA" technology because the tools allow genetic material to be manipulated or recombined. These techniques give scientists the ability to control gene expression, thus controlling production of proteins and biological compounds. Tools developed and commonly used in genetic engineering enable scientists to switch genes on and off and to direct gene expression to specific plant parts at specific times (Segal et al., 1999; Segal and Barbas, 2001; Guan et al., 2002; Ordiz, Barbas and Beachy, 2002; Stege et al., 2002; Koo et al., 2004).

Recombinant DNA technology, which allows genes to be controlled at will and with greater regulation than occurs in nature, leads to controlled production of proteins and biological compounds.

Bio-pharm crops typically are grown from genetically engineered seed. In another method, genes are introduced into a vector, such as a deactivated plant virus. This genetically engineered vector is manually rubbed onto a plant leaf, most often a tobacco leaf in early bio-pharming trials. The vector directs the plant to manufacture high levels of specific pharmaceutical protein in its leaves. This technology does not produce transgenic seed and the protein of interest is isolated in treated leaves, allowing further control over novel genes (Large Scale Biology, 2004b).

Altering the genetic makeup of crops is not new. For millennia, farmers have done just that through conventional plant breeding – the human selection and cultivation of sexually compatible plants with desirable features, such as faster growth, larger seeds or sweeter fruit. Even early plant breeding dramatically changed the genetic makeup of domesticated plant species compared to their wild relatives. Such changes accelerated as scientists began to understand dominant and recessive genes and, more recently, as they began using specialized pollination techniques and laboratory methods to create new cultivars (Gepts, 2002; Byrne, Ward and Harrington, 2003).

Plant genetic engineering is, in one sense, an extension of conventional plant breeding because it represents a continuation of people cultivating crops with desirable traits (Lemaux, 2001). But there are significant differences.

First, there's a difference in process. Transgenic crops acquire new genes through laboratory tools instead of pollination. The technology allows manipulation of specific genetic material, rather than the mixing of thousands of genes, and it allows control over where molecules of interest will be expressed in a plant – the seeds, for instance.

The new tools of plant genetic engineering also allow unrelated organisms to serve as gene donors as a way to introduce unique traits. For example, a single insect-resistance gene from the bacterium *Bacillus thuringiensis* has been transferred into corn to make what commonly is called Bt corn. By producing its own insecticide, Bt corn withstands common pests, such as the European corn borer and corn rootworm; that results in reduced need for chemical pesticide applications.

But bio-pharm crops are different even from other genetically engineered crops in the product they bear. These crops are grown solely as drug-production vehicles and are not intended as human food or livestock feed. The difference has policy implications. The unique qualities of bio-pharm crops could present economic-development opportunities, but also raise questions about potential risks (National Research Council, 2002; National Research Council, 2004a).

Economic development

With bio-pharming entering Colorado, now is an appropriate time for decision makers to consider whether the technology is right for the state and under what conditions. Important to that consideration is bio-pharming's potential contribution to economic development. Colorado likely will realize greatest economic benefits from bio-pharming if it attracts not only crop production, but research and development activity and processing facilities. Clustered and integrated operations involve more people and higher-paying jobs than cultivation alone, yielding economic resonance in the state (National Governors Association, 2003).

Some of Colorado's rural residents are interested in bio-pharming because they view the technology as a potential economic boon for struggling agricultural communities (Brand, 2004; Foutz, 2003; Hibbs, 2003). During Colorado Institute of Public Policy focus groups in spring 2004, many conventional farmers expressed hope that bio-pharming could be a springboard to better economic health for individual growers and their communities. Yet focus group participants across the state were unified in the opinion that attracting bio-pharm processing and related activities to rural Colorado is the best way to achieve widespread economic gains from the technology; they believed bio-pharm

cultivation alone would have limited economic benefit (See "Colorado stakeholders: insights, ideas and opinions" section and Appendix A for summaries).

Industry leaders emphasize this point. The Biotechnology Industry Organization, whose membership includes companies developing bio-pharm products, estimates that few farmers will be involved in bio-pharming even as the technology expands. Plant-made pharmaceuticals do not represent a new wave of value-added commodity agriculture, according to the organization (Biotechnology Industry Organization, 2002; Phillips, 2004). Bio-pharming requires very small acreages to produce large quantities of medicinal proteins, crops are grown under stringent regulatory conditions, and pharma farmers need technical training in cultivation protocols. These factors limit the number of farmers involved. "We have real concerns about making it seem that lots of farmers are going to have a new source of revenue," said Lisa Dry, Biotechnology Industry Organization director of communications. "We don't see that it's ever going to be a large market for farmers."[10] A Dow AgroSciences official noted that the need to carefully control seed distribution limits financial opportunities to a select group of highly trained growers who are either corporate employees or enter into close contractual relationships with biotech companies.[11]

Some influential Colorado farm groups nonetheless vigorously back bio-pharming, even though other industry and interest groups have opposed it. Alan Foutz, Colorado Farm Bureau president, is among the backers. Members of his group understand that financial gains from bio-pharming likely will be limited to a small number of farmers.[12] But for those growers, bio-pharming could be a profitable opportunity, Foutz said. The Colorado Farm Bureau also views small-scale cultivation as an important first step in attracting processing and related bio-pharm activities that might yield more widespread economic benefits. "We're not anywhere with those discussions until we begin to introduce a crop," Foutz said.

Such comments reflect the notion among some Coloradans that the state should participate in early bio-pharm field trials to establish itself in the industry, which could lead to notable economic benefits in the future. Others, however, have expressed a disinclination to bear potential risks from bio-pharm trials.

Just how many acres might be needed for bio-pharming? That's impossible to predict with a technology in its infancy. As one indication, Epicyte Pharmaceutical Inc. of San Diego has estimated that just 200 acres of genetically engineered corn could produce the same amount of pharmaceuticals in one year as a $400 million fermentation plant (Zitner, 2001).

The two Colorado bio-pharming proposals so far reviewed by federal and state officials illustrate a typical model of bio-pharm crop cultivation and show why direct economic benefits are probably limited for farmers. In both Colorado cases, Horan Brothers Agricultural Enterprises of Rockwell City, Iowa, planned to come in and cultivate pharmaceutical corn on Colorado's northeastern plains (Green, 2003).[13] In the field trial that moved forward, the Logan County landowner who leased a tiny plot for the state's first bio-pharm crop, and any local businesses that sold products and services associated with its cultivation, were likely the project's only immediate beneficiaries in Colorado.

A recent economic analysis suggests drug companies and consumers will gain most from plant-made pharmaceuticals (Kostandini, Mills and Norton, 2004). The case study focuses on potential effects of human serum albumin production in transgenic tobacco. Human serum albumin, an

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[10] Personal communication, Lisa Dry, Biotechnology Industry Organization director of communications, July 16, 2004.

[11] Bradley Shurdut, government and regulatory affairs for biotechnology, Dow AgroSciences, spoke at "Pharming the field: a look at the benefits and risks of bioengineering plants to produce pharmaceuticals," sponsored by the Pew Initiative on Food and Biotechnology, U.S. Food and Drug Administration, and the USDA Cooperative State Research, Education and Extension Service, pp. 25-26 of proceedings, retrieved February 9, 2004, from http://pewagbiotech.org/events/0717.

[12] Personal communication, Alan Foutz, Colorado Farm Bureau president, Aug. 18, 2004.

[13] Information from U.S. Department of Agriculture Biotechnology, Biologics and Environmental Protection Application for Permit number 04-131-01R filed by Dr. Kan Wang, Department of Agronomy, Iowa State University, May 5, 2004; and Application for Permit number 03-086-01R filed by Pierre Dorfman, Medical and Regulatory Affairs, Meristem Therapeutics LLC, March 14, 2003. Horan Brothers Agricultural Enterprises is described by the Colorado Corn Growers Association at http://www.coloradocorn.com/resources/media/pharm_backgounder.htm, with further information in Walsh and Redick (2003).

important blood protein, is now obtained from human blood plasma; global annual production totals about 500 metric tons, and global sales exceed $1.5 billion. Current estimates suggest world demand for human serum albumin could be met with 10,000 acres of transgenic tobacco. Market simulation indicates that adopting transgenic tobacco technology to produce the blood product would provide $43 million to $85 million in market surplus globally, through profits, increased efficiencies and lower costs for consumers. The share of economic benefit realized by consumers, producers and drug companies is complex, and depends in part on the market power of each group. The case study provides another indication that Colorado can capture greatest economic benefits from bio-pharming if it attracts processing facilities to reap benefits at each economic level – producer, consumer and pharmaceutical.[14] A similar analysis of genetically engineered corn and soybeans at Iowa State University found that, while farmers saw some financial gains, seed and chemical companies were the main economic beneficiaries of crop biotechnology (Duffy, 2001).

Several factors can influence the economic impact of bio-pharm processing in rural Colorado. Processing might offer significant and positive economic gains, partly because bio-pharm companies seek to capitalize on new areas of research and development and therefore might realize more profit than other rural firms (Falk and Lobao, 2003). Biotech firms could help diversify local economies and add to rural communities more capital resources and personal investments. Yet research suggests that policy makers carefully assess, on a case-by-case basis, needed investments and possible returns associated with potential economic development from bio-pharm processing. State agencies and university researchers have the ability to help rural communities with assessments critical to sound economic planning (Weiler, 2000).

The following factors help determine a community's capacity to capitalize on the new technology and a company's interest in investing in the community. These factors could be included in analysis of economic-development potential:

Firm structure: A company's organizational characteristics influence its economic impact. If a firm provides living wages and benefit packages, it might be a net benefit to the community. If the company has sufficient resources to cover its health and retirement liabilities, it might contribute to long-term economic and community vitality. Companies that promote or reward civic involvement by its employees contribute to building a strong sense of place and civic engagement.

Number of people employed and skills required of employees: A company that locates bio-pharm processing in Colorado likely will hire employees within the local labor market and also recruit workers from outside the market. The number of local workers hired will depend on skills available to safely and profitably process bio-pharm crops. Likewise, if a firm contracts with local farmers to grow bio-pharm crops, those farmers must be proficient in cultivation protocols required by state and federal agencies to offset potential risks. It is likely that biotech companies also will continue the current practice of contracting with outside farmers to cultivate bio-pharm crops.

Physical infrastructure needed: Biotech companies need physical infrastructure for bio-pharm processing. Requirements might include roads, telecommunications connectivity, and water, sewer and electrical service, among other needs. State investment might help rural communities meet industry requirements for physical infrastructure.

Economic infrastructure needed: Local companies provide goods and services – the economic infrastructure – that an incoming firm might need to conduct its business. A firm locating bio-pharm cultivation and processing in rural Colorado might rely on local agribusinesses to supply equipment, fuel, fertilizer and pesticides, among other necessary inputs. A biotech company headquartered outside the state might require comparatively little local economic infrastructure; it probably will not need, for instance, local financial services. But the firm's local employees need a range of commercial goods and

[14] The market simulation by Kostandini, Mills and Norton (2004) conservatively assumes pharmaceutical companies have a low degree of market power in both the transgenic tobacco market and the human serum albumin market; it also assumes a unit cost reduction of 15 percent.

services, from groceries to banking. There could be significant and unexpected economic-multiplier effects from an increase in local commerce.

Social infrastructure needed: Employees of local bio-pharming operations, like other community residents, will need social resources. These resources include public schools, institutions of continuing or higher education, churches, public-safety agencies, health services and cultural venues. It is important to assess needs for social infrastructure because some companies have proved a drain on Colorado communities, needing resources not fully defrayed by contributions to the tax base. Conversely, some relocating companies have provided rural Colorado communities with resources to improve social infrastructure for all local residents.

Other community contributions: Companies not only fulfill roles as employers, providing wages and benefits for local residents, but also function as corporate citizens. In the latter role, a biotech company might add to a community's well-being by sponsoring civic events, donating to local projects and offering mentorship programs for local students, among other contributions.

An incremental approach

Focus groups in Walsh and Sterling, on the state's Eastern Plains, discussed small-scale cultivation as a possible first step to attracting bio-pharm processing. These stakeholders generally regarded locally integrated bio-pharming activity as a potential tool for economic development. Some meeting participants reasoned that an incremental approach could engender public confidence in bio-pharming and provide the foundation for economic development, ultimately building to a more widely profitable production model. Meeting participants generally agreed that locating processing near fields could add to the safety of plant-made pharmaceutical production, which might persuade drug companies to put processing in rural Colorado. Some meeting participants expressed interest in forming a bio-pharming partnership, with growers contracted to supply crops to a biotech company, which would process crops locally. Such a business model is characterized by shared profits and shared financial risks.

Models for economic development

Blue Sun Biodiesel, an agricultural energy company based in Fort Collins, presents a Colorado business model to illustrate how such partnerships might work. Blue Sun produces and distributes diesel fuels derived from oilseed crops.[15] It contracts with two farmer cooperatives formed to invest in the company and supply its crops. Blue Sun's principals market and distribute biodiesel products; its farmer-suppliers in Colorado, Nebraska and Kansas share profits. The company taps university expertise through crop trials at research stations. Blue Sun has landed federal grants, including one to support rural economic development. It is important to note that Blue Sun Biodiesel's value-added business model involves financial risks, but it does not involve the safety issues and stiff regulatory requirements unique to plant-made pharmaceuticals and industrial compounds. Those issues and requirements might preclude application of this business model to bio-pharming.

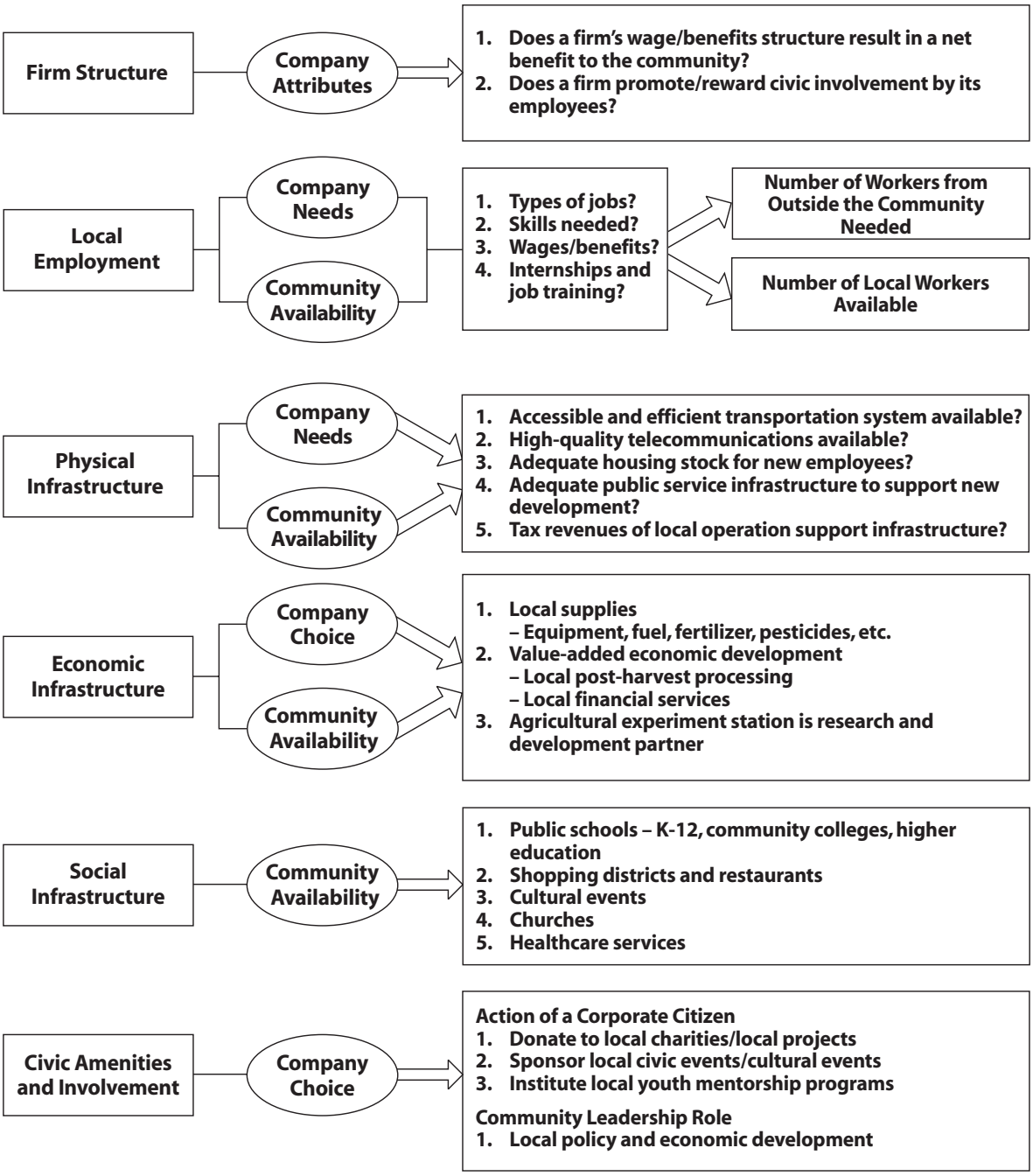
Dow Chemical Co. provides a partnership example in the research and development phase of bio-pharming. In February 2004, Dow Plant Biopharmaceuticals and NOBEX Corp. announced they would collaborate on plant-based production of a peptide developed as a potential appetite suppressant to treat obesity (Dow Chemical Co., 2004; Sheridan, 2004). NOBEX is providing a proprietary gene sequence for use with plant-expression technology developed by Dow Plant Biopharmaceuticals. The companies hope laboratory testing will lead to a plant-derived appetite suppressant. Applied to Colorado, such a partnership model might involve an outside company pursuing plant-made pharmaceutical technology and an in-state biotechnology company whose work could help lead to a fully commercialized product.

[15] Personal communication, Jeff Probst, Blue Sun Biodiesel president and chief executive officer, Aug. 4, 2004; company information available at http://www.gobluesun.com.

A framework for assessing bio-pharm benefits: economic-development potential

Understanding the potential for economic development from bio-pharming involves case-by-case analysis of required investments and potential community returns. The framework provided here is a chart (See Figure 3) to assess important factors involved in economic development. Communities can determine the relative importance of required investments and potential returns. A proposed bio-pharming project might be of interest to a community if overall benefits meet economic-development goals and outweigh costs incurred to fulfill a company's infrastructure needs.

Figure 3: What is the potential for economic development?



Getting from here to there: the role of stakeholders in economic development

In September 2003, a group of Colorado legislators and agricultural leaders visited Meristem Therapeutics operations in France. Some returned enthusiastic about the potential economic benefits of attracting bio-pharm crop cultivation and processing to Colorado (Carman, 2003; Porter, 2004). But how might the state and interested communities get from here to there? How might Colorado go from growing a fraction of an acre of bio-pharm corn to attracting the integrated research and development, cultivation and processing that might deliver greater economic benefits?

Stakeholder input – including public input – could be central to the decision-making that will shape bio-pharming's future in Colorado. Why? There is sometimes a rush to capture perceived benefits of new technology, which can lead to problematic economic, ecological and political issues that might be anticipated, addressed and allayed through stakeholder participation.

There's a related reason public participation might be an indispensable part of bio-pharm policy making and regulatory formation and reform: Public acceptance is critical to the advancement of new biotechnology. Yet the public often poorly understands or mistrusts biotechnology. If the public participated in decision-making, policy makers and regulators could provide key information about bio-pharming to all stakeholders, gather from stakeholders valuable insights into the technology and its possible effects in Colorado, and determine whether bio-pharming is right for the state and its communities. Public participation can help policy makers and regulators lay appropriate groundwork for the technology to advance, offering greatest benefits with fewest risks.

Colorado might best achieve constructive public involvement by allowing all stakeholders the means to review and communicate about bio-pharming and the policies that govern it. Those involved might include stakeholders interested in or affected by bio-pharming: state residents, bio-pharm companies, growers, landowners, economic-development experts, interest and industry groups, and university researchers, among others.

Stakeholder involvement in decision-making might address public acceptance of bio-pharming and its economic benefits in three key ways:

- By encouraging policies and regulations that support bio-pharming operations and economic development while also protecting public interests;
- By providing reliable information in response to public concerns; and
- By identifying needed investments in infrastructure and research and development, or other incentives, to advance bio-pharming technology and meet the economic-development needs of Colorado communities (Bartik, 1994).

With this tri-pronged focus, stakeholders promote policies and regulations that respond to public concerns about an evolving biotechnology while encouraging its judicious and sustainable growth (Organisation for Economic Co-operation and Development, 2004).

This approach to bio-pharm policy and regulatory formation draws on proven strategies for rural community development. It incorporates a willingness to invest in the future; stakeholder participation in community decision-making; realistic appraisal of future opportunities; awareness of competitive positioning; knowledge of state and local resources; active economic development; sophisticated use of information resources; and willingness to seek outside help (Luther and Wall, 1998).

Decision makers will choose the mechanism for stakeholder involvement in Colorado. An option to consider is formation of a policy council to engage the public and private sectors in benefit

and risk analyses, as well as strategic planning. Such a policy council might operate under the auspices of the Colorado Department of Agriculture, or another appropriate state agency, and be linked to, or modeled upon, the state's Biotechnology Council or Colorado Agricultural Commission.[16] The Colorado Department of Agriculture has a Biotechnology Technical Advisory Committee made up of researchers from Colorado State University and University of Colorado. They review state bio-pharming applications and advise the department about technical aspects of the proposals. This committee would be logically linked to any larger concerted effort.

Colorado's institutions of higher education might help the state capitalize on bio-pharming in several other ways:

- By conducting research to discover new bio-pharm applications, to develop safe and effective production methods, to understand economic impacts, and to improve benefit and risk assessments;
- By establishing incubator programs that help university researchers move discoveries to commercialization;[17]
- By educating mid- and upper-level company employees who need technical expertise in genetic engineering, risk management, agronomy, pest management, bioprocessing and other relevant fields;
- By delivering training programs for farm workers on cultivation protocols for bio-pharm crops; and
- By providing research-based information to stakeholders about the technical aspects of bio-pharming, its potential benefits and its potential risks.

Bio-pharming safety issues

Many people are excited about bio-pharming's potential to boost human health and local economies, and the benefits of this emerging biotechnology might indeed be great. Yet bio-pharming presents safety issues that are a necessary part of analyses and policy discussion. These issues arise because plant-made pharmaceuticals are not controlled like proteins cultured in enclosed fermentation facilities (Peterson and Arntzen, 2004).

A bio-pharm crop's unique genes could potentially spread to wild or domesticated relatives through pollen or seed, a process called "gene flow." Likewise, plant material containing pharmaceutical proteins could accidentally enter the human food or livestock feed supply through commingling during harvest, transport or storage. Such possibilities are the focus of a growing body of research, bio-pharming regulations, and much of the debate over this biotechnology.

Risks related to gene flow and commingling were the primary focus of discussion at the four focus groups held by the Colorado Institute of Public Policy. Participants in all state quadrants made clear that they want information addressing their risk-related questions before they would feel comfortable with scaled-up bio-pharming activities in Colorado.

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[16] The Colorado Biotechnology Council, attached to the Governor's Office of Innovation and Technology, works "to enhance Colorado's existing life science industry. The Council shall develop a vision for the future of the industry, market existing activities, and serve as a single point of contact for the industry. The Council may examine economic development, business and legislative issues crucial to the vitality of this industry." Information at: http://www.oit.state.co.us/commissions/biotech.asp. The Colorado Agricultural Commission of the state Department of Agriculture, is "responsible for making recommendations to the Commissioner, the Governor and the General Assembly regarding agricultural issues within the state; developing policies for preparing and enforcing rules and regulations related to agriculture; reviewing and approving all rules and regulations before release by the Commissioner or agriculture department's divisions; developing general policy for managing the agriculture department; and approving and monitoring the agriculture department's budget." Information at: http://www.ag.state.co.us/commissioner/ag_commission.html.

[17] The Colorado State University Research Foundation, for instance, has a commercial opportunity fund; faculty may apply for grants to develop technologies for commercial application. CSURF also refers Colorado State faculty to the Fort Collins Virtual Business Incubator for help moving discoveries to commercialization. Information at: http://www.csurf.org/enews/February2004/commercial_fund.html.

Bio-pharm gene flow

Gene flow – the exchange of genetic material through pollen and seed – is a natural occurrence that is not unique to genetically engineered plants. In the world of living creatures, gene flow is as old as life itself. It happens any time one organism breeds with a related species, thus passing along their combined DNA to offspring (Pew Initiative on Food and Biotechnology, 2003b). In the context of bio-pharming, this raises important issues for policy makers, regulators and stakeholders. If Colorado residents and decision makers decide to pursue bio-pharming, protocols should be established and effectively used to confine gene flow in open-field bio-pharm production systems, or to contain gene flow in greenhouse production systems.

Pollen, which carries the male half of genetic material, often is dispersed to other plants by wind and insects; the interplay of plant reproductive parts and dispersal agents might lead to hybrids, in which distinctive genes might persist for generations in some plant species (Whitton et al., 1997). Self-pollinating plants shed less pollen within an enclosed floral structure and do not rely on wind and insects for reproduction, meaning the pace of gene flow is slower, but not halted, when these plants are involved.

The expanding field of plant biotechnology has drawn new attention to pollen movement, gene flow and hybridization for obvious reasons: The spread of novel genes has the potential to alter the genetic makeup of wild and domesticated plants, and to enter the food and feed supply (Ellstrand, 2001; Boerboom, 2002; Morrison et al., 2002; Snow, 2002; Ellstrand, 2003a). It is clear that isolation distances recommended for seed production are insufficient to effectively control the novel traits expressed in bio-pharm crops (National Research Council, 2000). For example, Rieger et al. (2002) detected cross-pollination in canola, a member of the mustard family, at a distance of about 1.5 miles, whereas the isolation guideline for seed production in mustard species is 0.25 miles.

Gene-flow is further complicated because pollen and seeds are dispersed differently depending on species and growing environment. For instance, a study of pollen dispersal from genetically engineered bentgrass showed that wind carried the lightweight pollen much farther than previously known, allowing the bioengineered grass to pollinate wild grass of a different species nine miles away and to pollinate grass of the same species 13 miles away (Pollack, 2004; Watrud et al., 2004). For this reason, several questions must be carefully addressed on a case-by-case basis – with each proposed bio-pharm crop – to better understand gene flow and its implications (Ritala et al., 2002):

- How much pollen and seed does the plant produce?
- How far can the pollen be carried by wind or insects?
- What domesticated, wild or weedy relatives are in the area with which the plant could potentially outcross?
- Would the pollen be viable if it reached sexually compatible plants either in other farm fields or in the natural environment?
- If a bio-pharm crop successfully cross-pollinated other plants, would hybrids express genetically engineered traits? Would those novel traits persist in subsequent generations of so-called spontaneous hybrids?

There are data on pollen drift for corn and other crops in some parts of the United States and other countries, but a relevant data set for Colorado is incomplete. To fill the gap, Colorado State University researchers, in collaboration with growers and others, have begun studies to determine the extent of pollen drift in corn, wheat and sunflower.

Pollen studies in corn are most advanced, with data collected from sites in Boulder and Morgan counties in 2002 and 2003.[18] Plots of corn with marker traits, either blue kernels or herbicide

[18] Unpublished data about Colorado State University pollen drift studies are from Dr. Patrick Byrne, principal investigator and associate professor, Department of Soil and Crop Sciences.

tolerance, were planted adjacent to corn lacking the traits. At harvest, grain samples were collected at distances ranging from 2.5 feet to 1,000 feet from the source plots. Cross-pollination was determined by counting colored kernels or evaluating herbicide tolerance. As expected, the amount of cross-pollination dropped off rapidly with distance: By 150 feet from the plots with marker traits, less than 1 percent cross-pollination was observed in all trials. The farthest distances at which marker traits were detected were 600 feet, 583 feet, 375 feet and 270 feet in the four trials. Wind variation during pollen shed helped explain the spatial pattern of cross-pollination at some locations but not others, indicating that other field- or hybrid-specific variables were also involved. This work is continuing in 2004 at four sites, including one on Colorado's Eastern Plains, where bio-pharm crops are most likely to be grown. The goal of this project is to develop a predictive model of corn pollen dispersal under a range of meteorological conditions representative of Colorado.

In wheat, a U.S. Department of Agriculture grant is funding a three-year Colorado State study to estimate the level of pollen drift in commercial-scale plantings. The study will investigate gene flow from wheat to wheat, and from wheat to jointed goatgrass (*Aegilops cylindrica*), a weed species that can cross-pollinate with wheat. Wheat is not an immediate target for production of pharmaceutical or industrial proteins, but it may be relevant in the future.

Sunflowers genetically engineered to produce rubber are being evaluated in contained facilities at the Colorado State University Agricultural Experiment Station's Western Colorado Research Center at Fruita.[19] These rubber-producing sunflowers would fall under the same USDA regulatory framework as crops producing drugs. The USDA has funded a companion study, which began in Fruita in 2004, to estimate pollen drift in sunflowers; this study is expected to provide relevant risk-assessment data for the potential field testing of rubber-producing sunflowers.

Bio-pharm commingling

Gene flow is not the only concern. Plant material containing pharmaceutical or industrial proteins could unintentionally mingle in human food or livestock feed supplies. Plant seeds containing novel traits have accidentally mixed with commodity crops in two highly publicized incidents, illustrating the possibility for such commingling (Taylor and Tick, 2003).

In September 2000, StarLink™ corn,[20] produced by Aventis CropScience of France, was detected in the human food supply. Subsequent studies by the U.S. Environmental Protection Agency and federal Centers for Disease Control and Prevention found no evidence of allergic reaction among people who unwittingly ate StarLink corn. This particular version of Bt corn was engineered with a gene from the *Bacillus thuringiensis* bacterium to resist the European corn borer. StarLink corn had been approved by the EPA only for animal feed and industrial use, not for human consumption, because tests did not rule out the possibility for allergic reaction if the corn were eaten by people. But Genetically Engineered Food Alert, a coalition of consumer and environmental groups, discovered evidence of StarLink DNA in taco shells. Traces of the genetically engineered corn later were found in a number of corn products, from chips to corn dogs. Even though there was no evidence of allergic reaction, the incident triggered massive food recalls, lawsuits from consumers, regulatory change, temporary closure of grain mills and significant impacts on international markets for commodity corn (Taylor and Tick, 2001).

In November 2002, federal inspectors announced they had detected bio-pharm corn mingled in commodity soybeans in Nebraska. The bio-pharm corn had been genetically engineered by ProdiGene Inc. of Texas to produce an experimental vaccine for use against a viral disease in pigs. The commingling apparently occurred because bio-pharm corn seed remained in the field after harvest and sprouted the following season in a soybean crop in the same field. These "volunteer" corn plants

[19] Personal communication, Dr. Calvin Pearson, Colorado State University Agricultural Experiment Station, Western Colorado Research Center at Fruita.

[20] StarLink is a trademark for several genetically engineered corn hybrids produced by Aventis Crop Science, a German-French life sciences consortium.

were not destroyed, in violation of U.S. Department of Agriculture regulations, and were harvested along with the soybeans. The U.S. Animal and Plant Health Inspection Service ultimately impounded and destroyed 500,000 bushels of contaminated soybeans stored at a grain elevator to prevent plant-made pharmaceuticals from moving through food or feed distribution chains. ProdiGene paid fines and clean-up fees totaling $3.25 million and posted a $1 million bond. Important to the case, USDA officials determined the mingling posed no safety risks for consumers. In a related ProdiGene incident, federal officials ordered a farmer to destroy 155 acres of corn grown in Iowa because it could have been cross-pollinated by the company's bio-pharm corn in a nearby field. As in the StarLink incident, the ProdiGene events provoked a variety of reactions, this time from the biotechnology industry, food processors, consumer advocates, politicians and farmers interested in pursuing bio-pharming (Animal and Plant Health Inspection Service, 2002; Zinnen, 2002; Fox, 2003; "ProdiGene fined," 2003; Jaffe, 2004).

The cases illustrated not only the potential for commingling, but the role of human error in bio-pharm risks. In the ProdiGene case, federal regulators and others said bio-pharm safety measures and mandated inspections prevented pharmaceutical corn from moving through distribution chains; detractors were not convinced that protocols were adequate.

A different safety issue – the possible leaching of novel proteins from bio-pharm plants into the environment – is unlikely to be considered a concern. The pharmaceutical and industrial proteins in bio-pharm crops are directed through genetic-engineering techniques to be expressed in specific plant organs – the seeds, for instance – and, until processing occurs, the proteins remain tightly housed in those plant parts with help from cellular structures (Conrad and Fiedler, 1998).[21] This differs from other biotech crops, such as those expressing insect resistance, in which novel proteins are designed for expression throughout the plant.

Bio-pharming risks: assessing the implications

Scientific research shows that gene flow can occur from transgenic plants, and experience shows that plant parts expressing genetically engineered traits can inadvertently commingle with commodity crops bound for human food or livestock feed. The question is: So what? What are the implications of unintended flow and mingle involving crops with novel traits? Further, are those risks, including the costs of mitigating them, worth potential economic-development benefits?

Risks will not be the same for all bio-pharm applications, but will vary depending on the pharmaceutical protein in question, the crop in which it is produced, and the environment in which the crop is grown.

Risk analysis is critical to understanding what bio-pharming might mean for Colorado and its communities. Bio-pharming risk assessment, aimed at setting aside emotion and reaction in favor of relevant and reliable information, is the objective of recently initiated research expected to help inform bio-pharm regulations and safeguard the food supply, environment and agricultural markets (Iowa State University, 2003; "Researchers developing risk analysis tool," 2003; Montana State University, 2004; Wolt, 2004). Evaluating risk is fundamental to designing successful mitigation strategies; the two necessarily go hand-in-hand.

In discussing risk, the scientific community has drawn distinctions between genetic-engineering methods and products. Many scientists believe the process of manipulating genes with recombinant DNA techniques is not inherently dangerous. But in many cases, the same scientists think products of genetic-engineering technology – including some biotech crops and their novel traits – warrant increased scrutiny to ensure safety for human, animal and environmental health (National Research Council, 2002; National Research Council, 2004b).

[21] Personal communication, Dr. Andrew Staehelin, University of Colorado Department of Molecular, Cellular and Developmental Biology and a member of the Colorado Department of Agriculture's Biotechnology Technical Advisory Committee.

There is a growing call for rigorous bio-pharm risk analysis before crop cultivation or related activity begins, a call echoed by participants in focus groups held by the Colorado Institute of Public Policy. In a report called "Environmental Effects of Transgenic Plants," a National Research Council committee strongly advocated advance risk assessment involving the public. The committee argued that stakeholder participation in risk analysis increases public confidence in agricultural biotechnology and helps decision makers understand the significance of risks associated with transgenic plants (National Research Council, 2002).

One reason for careful analysis is that plant-made pharmaceuticals are not meant as food, and are not designed for human use unless they have been processed, purified and provided as therapy. Under the federal Food, Drug and Cosmetic Act, the presence of non-food material in food or feed products could cause those products to be classified as adulterated, regardless of whether the material actually poses health risks (U.S. Department of Health and Human Services, 2002). This regulation creates a standard of zero tolerance for the unintended presence of bio-pharm products in food or feed.[22]

It is useful to consider risks arising from bio-pharming in at least three broad categories: human-health risks, environmental risks and market-related risks. All are pertinent because of potential for bio-pharm gene flow and inadvertent commingling.

Human-health risks

Allergic reaction – when a compound provokes a hypersensitive response from the body's immune system – could be a risk of accidentally eating, having skin contact with, or unwittingly breathing some plant-made pharmaceuticals. For Colorado stakeholders and decision makers, these potential risks are relevant in the context of bio-pharm field trials, possible inadvertent commingling in food or feed supplies, and crop processing.

If bio-pharmaceutical proteins were unintentionally eaten because of commingling, they probably would be consumed in low amounts and would be broken down and inactivated during digestion. But protein alteration in the gastrointestinal tract does not completely eliminate risk of allergic reaction because of structural characteristics of some plant-made proteins (Metcalfe, 2003). For instance, some plant-made proteins might possess sugar components that could elicit allergic or immune response (Bakker et al., 2001). Pharmaceutical producers will need to develop appropriate tests for antigenicity; such tests can be constructed for compounds known to provoke immune-system reactions among people (Nordlee et al., 1996; Birdsley-Jensen and Poulsen, 1997).

Toxicity is a possible risk factor especially relevant in the context of potential occupational exposure; possible risks could be considered for farm workers, processing employees and others who might be potentially harmed.

If preliminary tests for allergenicity and toxicity show potential human-health risks with a bio-pharm proposal, safeguards could be used to mitigate those risks.

Some Colorado residents are concerned about the potential health risks associated with bio-pharm field tests. In light of that concern, Colorado decision might consider ways to communicate information about bio-pharm safeguards and their effectiveness. Colorado leaders might also find ways to ensure safety and to ensure that state residents have answers to their relevant safety questions as bio-pharm tests move sequentially from laboratories into production systems. Moreover, decision makers might want to satisfy themselves and their constituents that bio-pharm tests are safe even in the face of possible human error. The state might want to decline a bio-pharm proposal if the variables involved present more risk than benefit – or if the costs to mitigate risks tend to outweigh benefits for Colorado.

[22] Plant-made pharmaceuticals and the "zero tolerance" issues raised in federal regulations were debated by scientists and industry leaders during the panel discussion "The future of pharming: Can it be done safely?" (Center for Science in the Public Interest, 2002).

Focus-group participants had specific suggestions that might be used to address some health concerns. All participants indicated they will more likely accept bio-pharm crops deemed to present few possible threats to human health. For instance, many discussion participants indicated they would accept bio-pharm corn producing the enzyme lipase, which is secreted into the gastrointestinal tracts of all healthy people, if it were carefully regulated. Participants at a meeting in Durango advocated bio-pharm crop cultivation only in greenhouses, instead of open fields, to contain novel proteins and genes; some meeting participants viewed pharmaceutical production in food crops as generally riskier than production in non-food crops because of a greater perceived potential for commingling.

Environmental risks

Bio-pharm gene flow or seed escape could pose environmental risks; the degree of risk depends on a crop or hybrid's ability to grow and survive in natural ecosystems, and on the genetic trait conferred.

One environmental concern with bio-pharm crops surrounds potential for cross-pollination with wild or weedy relatives, which could create in the ecosystem a wild, hybrid plant perhaps capable of producing pharmaceutical or industrial compounds.[23] Some researchers have questioned whether inadvertent gene flow from transgenic crops to related domestic crops or wild plant populations could result in undesirable invasive characteristics (Snow and Palma, 1997; Ellstrand and Schierenbeck, 2000). Discussion of this possibility has centered on transgenic crops expressing insect resistance and herbicide tolerance, not on bio-pharm crops.

Bio-pharm crops might present ecological risks if their novel traits could be passed to other plants, and if those novel traits conferred a fitness advantage to other plants (Snow et al., 2003). In a natural environment, a gene associated with a fitness cost – meaning a gene that makes it harder for a plant to survive – is not likely to persist long-term in the environment (Baucom and Mauricio, 2004). However, there is a possibility that genes conferring to a plant neither an advantage nor a disadvantage in natural selection, known as "selectively neutral" genes, could endure for some time in a wild population, especially if there were ongoing gene flow (Ellstrand et al., 1999).

The possibility of unintended bio-pharm crop consumption by wildlife, livestock and pets presents another set of risk issues. Like human health, animal health should be considered when assessing the potential risks associated with a proposed bio-pharm crop, the compound produced and the conditions in which it is grown.[24] Bio-pharm crops grown in open fields could be consumed by a variety of Colorado wildlife, including geese, deer, raccoons, mice and insects, animals considered non-target species for plant-made pharmaceuticals. Also, wildlife could aid unintentional gene flow by transporting seeds to other environments, where those seeds – if still viable – could sprout with unintended results. Risk abatement would be important to addressing these and other potential risks.

Market-related risks

There could be economic consequences of bio-pharm gene flow and commingling. These possible economic risks could include potential impacts on agricultural markets, both niche and commodity markets, and potential legal liabilities resulting from a bio-pharm mishap.

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[23] Environmental risks potentially posed by bio-pharm crops were outlined by Dr. Norman Ellstrand, gene-flow researcher, genetics professor and director of the Biotechnology Impacts Center, University of California-Riverside. He spoke at "Pharming the field: A look at the benefits and risks of bioengineering plants to produce pharmaceuticals," sponsored by the Pew Initiative on Food and Biotechnology, U.S. Food and Drug Administration, and the USDA Cooperative State Research, Education and Extension Service, pp. 31-32 of proceedings, retrieved February 9, 2004, from http://pewagbiotech.org/events/0717.

[24] Dr. Charles Rupprecht, of the National Center for Infectious Disease, Centers for Disease Control and Prevention, discussed potential risks of plant-made pharmaceuticals for wildlife, and how those risks might be measured, at the Plant-Derived Biologics Seminar organized by the federal Food and Drug Administration and federal Animal and Plant Health Inspection Service, April 5, 2000, at Iowa State University. Proceedings available: www.fda.gov/cber/minutes/plnt1040500.pdf. Personal communication, Dr. Mowafak D. Salman, professor and director, Animal Population Health Institute, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Aug. 20 and Aug. 23, 2004; personal communication, Dr. Franklyn B. Garry, professor, Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Sept. 1, 2004.

Market loss from seed escape or crop-to-crop gene flow – a possible negative consequence for existing crop markets – could be among the most important risks of bio-pharming (Ellstrand, 2001; Pew Initiative on Food and Biotechnology, 2003b). Concern about the potential market-related impacts of bio-pharm crops was high among organic farmers, seed-stock producers and conventional farmers who attended focus groups (See "Colorado stakeholders: insights, ideas and opinions" section and Appendix A for summaries).

Organic and seed producers must meet very high and specific standards for purity, and failure to do can markedly lessen, or even ruin, crop value (Dechant, 2003). Organic producers, in particular, have voiced concern about the possible impact of all transgenic crops on their markets because U.S. Department of Agriculture standards exclude recombinant DNA technologies from use in organic farming. This concern was recently detailed in a survey of about 1,000 organic growers in the United States (Walz, 2004). Of the farmers surveyed, 46 percent indicated they view as moderate to very high the risk that genetically modified organisms will contaminate their organic products; 48 percent indicated they have taken measures to prevent contamination; 27 percent indicated they have been asked to test for the presence of genetically modified organisms; and 55 percent indicated that current regulations do not adequately protect their products from transgenic contamination. Some Colorado organic farmers said during focus-group meetings that the mere presence of bio-pharm crops in the state could negatively affect their markets because of buyer concerns about crop biotechnology.

Conventional farmers, including those in Colorado, also have described potentially serious financial impacts from inadvertent spread of bio-pharm genes or seeds to other crops. There could be an immediate impact on the value of the affected crop, and a secondary impact on crop demand. This was a point of serious discussion at bio-pharm focus-group meetings in Walsh and Sterling.

The market-related risks of bio-pharm gene and seed spread are significant when viewed in the context of global export markets. Transgenic crops are less accepted in other countries than they are in the United States, and leading importers of U.S. commodities in Europe and Asia have imposed import restrictions and strict safety-testing and labeling requirements for genetically modified food (Benbrook, 1999; Hanrahan, Becker and Jurenas, 2002; European Commission, 2004).

The ProdiGene and StarLink cases illustrated some of the financial consequences of transgenic commingling with commodity crops (See case descriptions on the section "Bio-Pharming Safety Issues"). The StarLink incident had unprecedented results because transgenic corn intended only for feed or industrial use not only entered the human food supply, but spread through national and international supply channels, disrupting agricultural trade (Segarra and Rawson, 2001). The case illustrated the costs of market loss for many American farmers, whether or not they grew the transgenic corn, the costs of massive food recalls, and the costs of mass tort litigation when a transgenic crop enters the food supply. Together, those costs were estimated to be $1 billion (Redick, 2003). The StarLink incident triggered declines in global demand for U.S. corn, which translated to millions of dollars in lost revenue for American corn producers (Schmitz, Schmitz and Moss, 2004). However, it is important to recognize that the scale and regulation of bio-pharm crop production and marketing would be very different from that of StarLink corn.

Public perception is an important factor to consider in the context of potential market-related risks from bio-pharming. Farmers who took part in Colorado Institute of Public Policy focus groups noted that market losses could potentially result solely from negative perceptions of bio-pharming safety issues – even with no evidence of hazard. Negative perceptions of biotechnology are a particular concern for export markets, participants said. The ProdiGene and StarLink cases illustrated the connection between perception of hazard and market loss: There was no evidence of harm to human health in either case, but markets suffered regardless. Most surveys have found that U.S. consumers have fairly positive attitudes toward biotechnology when they hear about benefits, but negative attitudes toward biotechnology have grown in recent years (Hoban and Kendall, 1993; Hoban, 1998; The Gallup Poll, 2001; Shanahan et al., 2001; Pew Initiative on Food and Biotechnology, 2002a). There has been a correlation between news of biotechnology mishaps and attitudes toward its use (Bruhn,

2003). European consumers, in particular, have negative attitudes toward crop biotechnology (INRA [Europe], 2002; McCullum et al., 2003). That has led to bans on some products from the United States (Scott, 2003).

The market-related risks of bio-pharming also encompass potential legal liability from inadvertent gene flow and crop contamination. Transgenic crop production raises legal issues including tort-based liability, such as that resulting from farmer vs. farmer lawsuits and consumer vs. farmer lawsuits; contract-based liability, involving biotech companies and farmers; and regulatory liability, from any violations of state and federal statutes or regulations (See Appendix C for description of potential claims, case law, articles and treatises). Legal precedent to help answer potential liability questions – the matter of who pays – is quite limited; courtroom battles could be on the legal horizon (Hamilton, 2003).

Some legal experts have argued that potential liability might be managed with establishment of state-mandated grower districts, which would segregate bio-pharm crops to further mitigate risks of gene and seed spread (Redick, 2003). Liability risk might also be managed with a carrot-and-stick approach driven by industry and aimed at market protection for all. With this approach, stakeholders create specific industry standards for plant-made pharmaceutical identity preservation, which would be contractually imposed through the chain of bio-pharming commerce and verified through third-party audits. Contracts include the threat of legal injunction for non-compliance to create further incentives for growers to prevent commingling (Walsh and Redick, 2003). Thomas P. Redick, chairman of the American Bar Association Committee on Agricultural Management, writes: "Given the global trend toward a precautionary approach to biotech crops, the stakes for building generally accepted identity preservation systems for bio-pharming could not be higher" (Redick, 2003, p. 13).

Intellectual property rights constitute another legal issue that has arisen with transgenic crops. In separate cases, the U.S. Supreme Court and the Canadian Supreme Court upheld the rights of biotechnology companies, Pioneer Hi-Bred International and Monsanto Corp., respectively, to fully control use of patented genes in genetically engineered plant varieties and seeds. Those rulings established intellectual property protections for transgenic seeds and plants, affirming the proprietary rights of biotech companies to patent an engineered plant gene and to control its use (Hamilton, 2003; Simon, 2004; Weiss, 2004).

The potential for sabotage of bio-pharm plots is an economic issue that concerned some farmers attending focus groups. That risk currently is mitigated because regulators do not release much of the information contained in bio-pharming permit applications on the grounds that it is proprietary information, generally referred to as "confidential business information." A push for greater transparency in bio-pharm regulations could mean that some information currently withheld from the public, including field location, might be available in public documents.

Frameworks for assessing bio-pharm risks: identifying issues and mitigation strategies

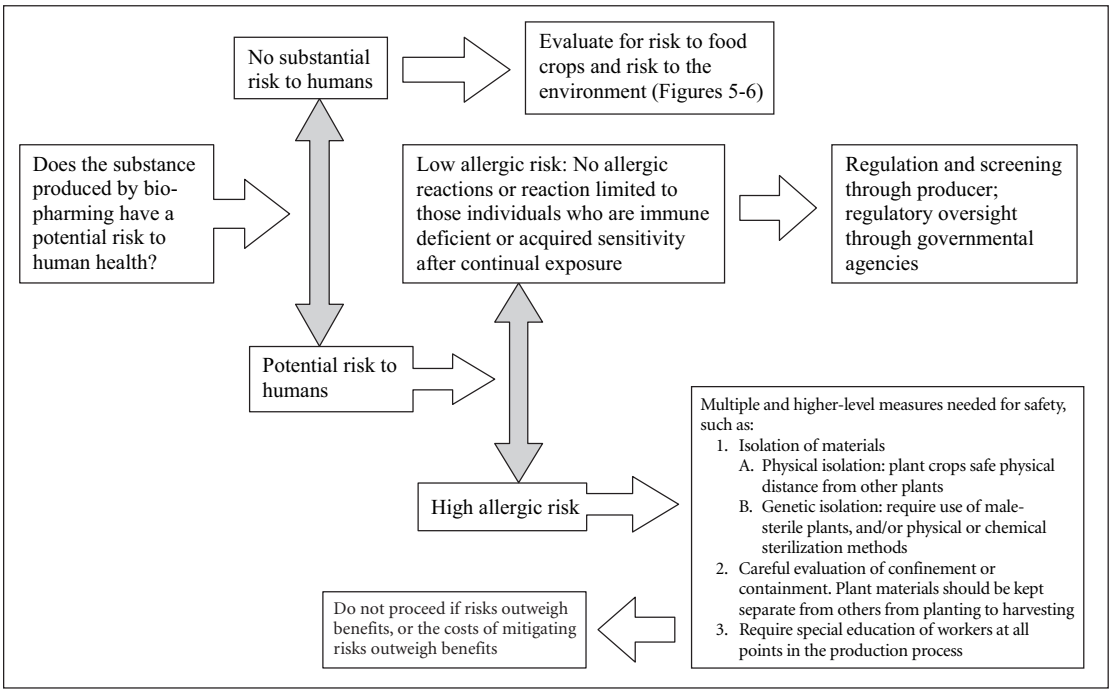
Bio-pharming risks should be assessed on a case-by-case basis with consideration for the crop, trait and environment (National Research Council, 2002).

Science-based risk assessment, employed on a case-by-case basis, can help communities determine what type of bio-pharm crops to consider, in what growing environments, and under what regulatory conditions (Peterson and Arntzen, 2004). Again, the state might want to decline a bio-pharm proposal if the variables involved present more risk than benefit – or if the costs to mitigate risks would tend to outweigh benefits for Colorado.

The risk-assessment frameworks provided here are flow charts meant to help decision makers understand and reach rational, fact-based decisions about bio-pharming in Colorado. Safety issues are separated into three categories (See Figures 4-6).

Figure 4: Does the plant-made protein pose potential risks to human health?*

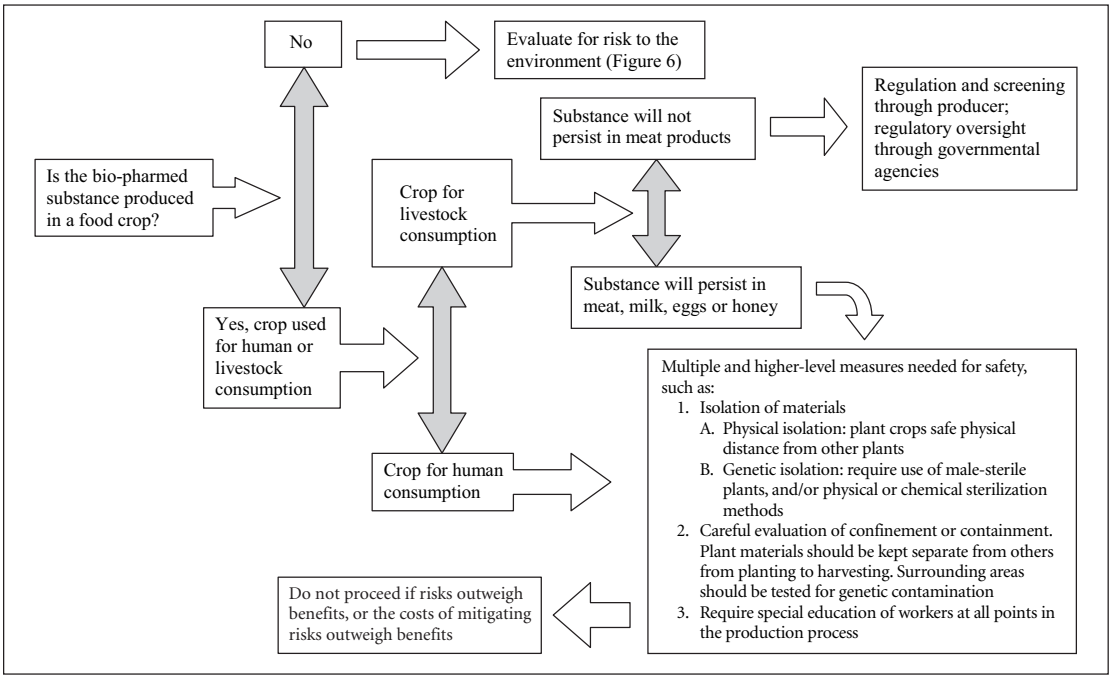
This framework assesses human-health risks, including potential occupational exposure for workers involved in producing and processing bio-pharm material.



* Gray arrows indicate places for application of logical, fact-based decisions about bio-pharming safety.

Figure 5: Is the plant-made protein produced in a food crop?*

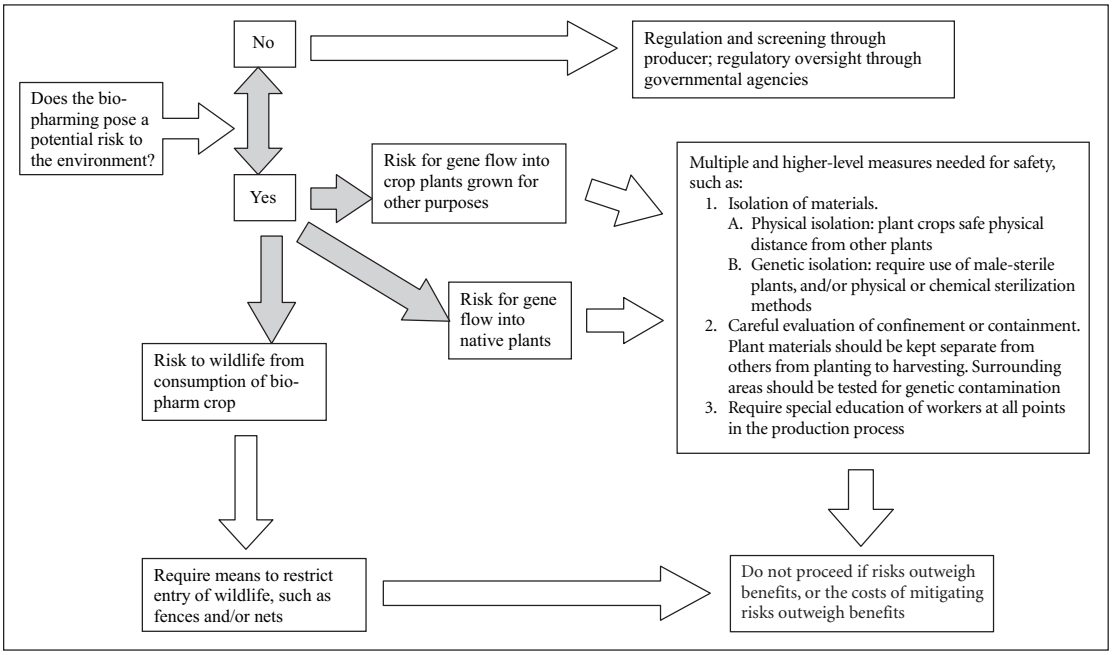
This framework considers unintentional bio-pharm impacts on food and feed supplies. For purposes here, "food crop" means a plant whose products are directly or indirectly consumed by humans or livestock for nutrition.



* Gray arrows indicate places for application of logical, fact-based decisions about bio-pharming safety.

Figure 6: Does the plant-made protein pose potential risks to the environment?*

This framework addresses potential bio-pharming risks for wildlife and risks of gene flow to crop plants and native plants. "Gene flow" means the unintended induction of the genetically engineered gene.



* Gray arrows indicate places for application of logical, fact-based decisions about bio-pharming safety.

Interpreting risk assessment: ethics and more

Risk assessment is central to considering how bio-pharming might be approached in Colorado. Yet risk assessment is not the last stop in the decision-making process.

In some cases, full assessment is limited by a lack of scientific data that might help fully determine risk probabilities, making bio-pharming risk analysis difficult. In particular, there is a dearth of interdisciplinary research on the ecological and agronomic effects of gene flow, and public investment in this research is needed (National Research Council, 2002; Snow, 2002).

In addition, any discussion of risk needs to involve the values of state residents because people assign meaning, or significance, to scientifically derived probabilities for risk and benefit. What is acceptable to some people and communities is not acceptable to others.

Two philosophies often emerge in bio-pharming risk discussions: the notion that risk is inherent in progress, and the notion that caution should prevail with many activities involving risk. The latter idea was developed into a political principle for action on environmental matters. Called the Precautionary Principle, it holds that people must proceed more cautiously with any activity that raises threats of harm to the environment or human health, even if some cause-and-effect relationships are not scientifically established. The proponent of an activity, not the public, bears the burden of proof in conditions of uncertainty (Ashford et al., 1998). The Precautionary Principle has become a central point of difference between Europe and the United States on biotechnology, and its application to biotechnology policy has been widely debated (Kaiser, 2002).

In the United States, there is a recognized approach for effectively addressing risk and societal judgments about the acceptability of risk; it applies to bio-pharming decisions. The approach involves three steps: recognition that risk is inherent in all technologies and processes; use of science-based

risk assessment to help weigh the balance of risk vs. benefit; and integration of science-based risk assessment with other perspectives on risk to arrive at a full understanding of risk, its consequences, its uncertainties and, importantly, its management.

Using this model, the values of Colorado residents could form an important ethical consideration in discussions about bio-pharming (Ellstrand, 2003b; Rollin, 1996a). Individual and community values help determine the significance and acceptability of risk-benefit probabilities assessed through science. In the context of bio-pharming, the principal ethical question asks: "How much benefit justifies how much risk?"

Science-based risk assessment is critical to decision-making because it ensures that decisions are grounded in facts. But decision-making on biotechnology might go a step further by accounting for public ethical beliefs regarding what benefits justify what risks (Rollin, 1996b). This requires some form of stakeholder involvement to help determine the conditions under which bio-pharming might be successfully pursued (Rollin, 1995a, 1995b, 1997).

The regulatory context

Once risks are identified, mitigating them becomes a critical issue; this is a regulatory purview. Federal regulations governing bio-pharming have received attention in the wake of the StarLink and ProdiGene cases and publication of the 2002 National Research Council Report, "Environmental Effects of Transgenic Plants," which was commissioned by the U.S. Department of Agriculture. The report called for more rigorous scientific risk assessment of transgenic plants on a case-by-case basis, regulations and regulatory oversight commensurate with established risks, more crop monitoring, and more public involvement in decisions. Since then, the federal government has begun regulatory updating that is still under way (Pew Initiative on Food and Biotechnology, 2002c; USDA, 2004; Witte, 2004).[25]

A flexible regulatory framework, which responds to changing conditions and new research-based information, can help achieve a balance between encouraging industry and protecting public health and the environment. Central to regulatory reform is determining whether current regulations are adequate for bio-pharm crops and, if not, what changes are needed.

Two federal agencies have primary responsibility for regulating bio-pharming (Nestmann et al., 2002):[26]

- **The Food and Drug Administration (FDA)**
    - The FDA ensures drug safety and efficacy. The agency must approve clinical trials and marketing for plant-made pharmaceuticals. The FDA also oversees manufacturing to guarantee consistent product quality and potency.
- **The U.S. Department of Agriculture – Animal and Plant Health Inspection Service (USDA-APHIS)**
    - Bio-pharm crops are subject to standard USDA-APHIS regulations for all genetically engineered crops, as well as additional oversight. Unlike other genetically engineered crops, those producing pharmaceutical or industrial proteins are subject to "perpetual permitting," meaning applications to cultivate must be submitted and granted annually. Regulatory reform is expected to further protect the environment, and food and feed supplies. Current regulations are meant to account for potential human error, and that regulatory underpinning is expected to continue. As part of reform, federal agencies in

[25] Agriculture Secretary Ann M. Veneman announced USDA's intention to update and strengthen its biotechnology regulations for genetically engineered organisms on Jan. 22, 2004. A transcript of remarks is available at http://aphisweb.aphis.usda.gov/lpa/issues/biotechcomp/Transcript_of_Biotech_7DB94.doc.

[26] For a detailed description of the roles of the three federal agencies, see the "Evaluation & Regulation" section of the web site "Transgenic crops: An introduction and resource guide" at http://www.colostate.edu/programs/lifesciences/TransgenicCrops/.

2002 issued the draft document "Guidance for Industry: Drugs, Biologics and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals" (U.S. Food and Drug Administration, 2002). In 2004, after announcing plans to impose more stringent conditions for bio-pharm field tests,[27] APHIS specified new information required on permit applications (APHIS, 2004a). Applicants are asked to detail the amount of novel proteins in all plant parts, the results of allergenicity testing, assessment of potential toxicity for non-target organisms, more information on confinement measures, and a description of employee training.

- Current USDA-APHIS risk-mitigation requirements for bio-pharm crops include:
  - All workers must undergo annual APHIS-approved training on special cultivation procedures.
  - Farmers must use dedicated equipment for planting and harvesting bio-pharm crops; this machinery cannot be used with any other crop. Tractors and tillage equipment must be thoroughly cleaned before being used for another purpose.
  - Dedicated, locked storage facilities are required for seed and farm equipment.
  - Bio-pharm crops must be isolated from related crops to reduce risk of cross-pollination. For example, bio-pharm corn must be isolated by at least 1 mile from other corn fields if it is open-pollinated, or by one-half mile if pollination is controlled through male sterility or detasseling.
  - A 50-foot perimeter of fallow ground, which is not used for crop production, must surround each bio-pharm crop.
  - No food or feed crops can be grown in the test plot or fallow zone the following year.
  - APHIS will closely monitor bio-pharm fields during the growing season and in following seasons to ensure that required procedures are being followed and that "volunteer plants" (those that sprout from seeds inadvertently left behind) are removed.
  - When considering permit applications, APHIS may take into account other strategies to contain gene flow and commingling – for instance, later planting dates, known as temporal isolation, that can reduce the potential impact of pollen shed on other plants.

The Environmental Protection Agency (EPA) regulates crops that have been genetically engineered to resist pests, such as those expressing Bt insecticidal proteins; at this time, the EPA has a role with bio-pharm crops only if those crops express pest resistance in addition to pharmaceutical and industrial proteins.

State departments of agriculture, such as the **Colorado Department of Agriculture**, also have a role in bio-pharming oversight. Agriculture departments may review developer permit applications after they have undergone preliminary assessment by APHIS. States have 30 days and four options for decision-making:

- Concur with APHIS assessments and conditions;
- Concur, recommending additional permit provisions;
- Not concur, with reasons;
- Not respond, in which case APHIS can proceed.

[27] See APHIS, 2003a, for the press release, and the linked PDF file "APHIS Federal Register Highlights" for comparison of the new regulations to the previous ones.

APHIS can legally issue a bio-pharm permit even if a state agriculture department does not concur; the agency is not obligated to add permit provisions suggested by state departments of agriculture.[28] However, federal regulators have said they want to work with states to understand and address any concerns about a bio-pharm permit application that elicits different responses at the federal and state levels.

After receiving its first bio-pharming proposal from Meristem Therapeutics in 2003, the Colorado Department of Agriculture (CDA) convened a Biotechnology Technical Advisory Committee of three university scientists, two from Colorado State University and one from the University of Colorado, to help review the first application and others to come. The panel is responsible for advising the state on gene flow and biosafety issues; the committee also questions applicants about crop management. The committee reviewed the Meristem application, interviewed company personnel, and discussed production plans with growers contracted to produce the crop (See description of the Meristem plan in "The Colorado Context" section). The CDA then concurred with the APHIS determination to grant a permit. But approval came late in the 2003 growing season, and Meristem did not proceed.

The CDA later published a draft document "Procedures for evaluating experimental biotechnology permits for plant-made industrial and pharmaceutical and products in Colorado," which formalizes the way permit applications are evaluated, invites public input, and lists what will be considered in CDA review of bio-pharm permit applications (Colorado Department of Agriculture, 2004).

The CDA received a second bio-pharm permit application, from Iowa State University, in 2004 (See description of the Iowa State plan in "The Colorado Context" section). After consulting with its Biotechnology Technical Advisory Committee, the CDA approved the permit application with two suggested provisions in addition to APHIS conditions: that the bio-pharm corn plants be detasseled before pollen shed to further minimize the possibility of cross-pollination with food or feed corn; and that ears on plants be covered with weather-proof paper bags after pollination to reduce the chance that birds or insects come into contact with developing seed. APHIS approved the application, but declined to impose the additional conditions, considering the standard conditions to be sufficient. The trial was planted in June.

With regulatory reform under way, stakeholders and state and federal officials are discussing, or might soon be discussing, a number of bio-pharming issues.

Possible reforms:

- APHIS is evaluating development of **regulatory tiers** that apply to transgenic crops according to established risks ("Environmental Impact Statement," 2004). This could streamline approval for low-risk crops while imposing more rigorous conditions for higher-risk crops. Such tiers might, for example, take into consideration toxicity levels, the plant tissues in which a novel compound is expressed, whether wild or weedy relatives are in the area of the test site, and whether a novel compound is produced in a food crop or a non-food crop.
- The **FDA and EPA** might have greater roles in reviewing bio-pharm permit applications for issues related to food safety and environmental risk (Pew Initiative on Food and Biotechnology, 2004a).
- APHIS likely will need **more staffing and expertise** to monitor bio-pharm field trials and enforce regulations, allowing its inspectors to make multiple visits to test plots during and

[28] Personal communication, Mitchell Yergert, chief of Plant and Insect Section, Colorado Department of Agriculture, Aug. 30, 2004.

after the growing season. A question for Colorado decision makers is whether adequate federal funding will be available for bio-pharm oversight envisioned now and in the future; that could have an impact on some risk-related issues in the state.

- APHIS might **re-evaluate the zero tolerance policy** for presence of plant-made pharmaceuticals in food and feed. Under the federal Food, Drug and Cosmetic Act, enforced by the FDA, the presence of non-food material in food or feed could cause those products to be classified as adulterated, regardless of the health risks (U.S. Food and Drug Administration, 2002). This regulation creates a standard of zero tolerance for adventitious presence of bio-pharm products in food or feed. The policy could trigger massive recalls if trace amounts of a bio-pharm substance were detected in food or feed supplies, even with no evidence that detected levels could result in harm to humans or livestock. If the zero tolerance policy is amended to allow for unintentional, intermittent and low-level presence of some compounds, the allowable presence would have to be defined for each product and a testing program likely would be created. APHIS has asked for public input on adventitious presence, opening questions about whether establishing tolerance levels for plant-made pharmaceuticals could protect both consumers and industry ("Environmental Impact Statement," 2004).
- APHIS might **re-evaluate what constitutes "confidential business information."** Some information about proposed bio-pharm crops currently is removed from public documents and is not available for review by either the public or state officials. This information, called confidential business information, comprises a range of details, including engineered genes and plot location. The practice of keeping some information secret is meant to protect the proprietary interests of companies developing products with patented genes; it also is meant to protect against vandalism and other potential problems. But lack of information hinders state officials trying to reach timely decisions about bio-pharm applications. The practice also prevents full public review of applications.
- APHIS might create **crop-specific cultivation guidelines** for individual crops, based on pollen, seed and other characteristics.
- State or federal officials might **increase the time** allowed for states to review bio-pharm permit applications. State departments of agriculture have 30 days to evaluate permit applications for genetically engineered crops expressing pharmaceutical or industrial proteins. This is little time to consult with technical advisors, receive public input and make decisions about bio-pharm proposals and any additional cultivation protocols appropriate to local growing environments.
- State or federal officials might **increase state authority** to review bio-pharm permit applications and require any additional cultivation protocols ("Environmental Impact Statement," 2004). Local officials might be best positioned to assemble important information about weather, soil, wildlife, cropping systems or other facts relevant to a bio-pharm cultivation site.[29]
- The Colorado Department of Agriculture might **incorporate toxicity data** into criteria used when considering bio-pharm permit applications, because APHIS does not currently consider information about toxicity testing of a plant-made pharmaceutical or industrial compound.
- State and federal officials are working to **seek more public input**, understanding that a transparent regulatory process incorporates valuable information about bio-pharming from the public and stakeholders, builds regulatory credibility and helps build public confidence in a new technology (Colorado Department of Agriculture, 2003; "Environmental Impact Statement," 2004).

[29] The Colorado State University Cooperative Extension Biotechnology Issues Team suggested that APHIS review its expectations of state departments of agriculture for field-test permitting, and revise procedures if necessary. This letter was in response to the USDA Federal Register announcement of proposed preparation of an Environmental Impact Statement on the regulation of genetically engineered organisms (Docket No. 03-031-2, Federal Register 69(15): 3271-3272). Letter available: http://www.ext.colostate.edu/staffres/biotech_usda.pdf.

Other risk-mitigation issues under discussion:

- Regulators and stakeholders are discussing the **pros and cons of enclosed cultivation settings and open-air crop cultivation** in farm fields. Enclosed settings, such as greenhouses, might reduce risks of gene flow and commingling, but open-air plots might present more favorable conditions for crop cultivation. APHIS also has asked for public input in its efforts to develop appropriate regulations for private-sector enclosed production systems ("Environmental Impact Statement," 2004).
- Regulators and stakeholders are discussing the **pros and cons of using food and non-food crops** in bio-pharming. Use of non-food crops might reduce risks of inadvertent bio-pharm commingling in the food supply, or at least public anxiety about those risks; but food-crop genomes are among the best-known, and these crops are among the most successfully cultivated ("Drugs in crops," 2004). Related discussion surrounds choosing plants that produce low pollen and seed.
- Researchers, regulators and stakeholders are examining **new ways to mitigate risks**. Under review are visual markers, such as differently colored seeds or plant tissue that could help identify any out-of-place plant material. Biologically based controls, known as "bioconfinement" techniques, are being sought to prevent gene flow and inadvertent commingling; examples include sterile pollen, sterile seed and tissue-specific deletion of transgenes (Daniell, 2002; Ellstrand, 2003b; National Research Council, 2004a). Likewise, controls are being sought to mitigate risks specific to a growing environment. For instance, to reduce risk of wildlife interaction with bio-pharm crops in open fields, growers might use unique fencing, netting, bagging or noise barriers.
- Regulators and researchers are discussing use of **validation testing and ecological monitoring** after planting or commercialization to make sure methods of mitigation are effective.

State legislation

Many states are using legislation to stake out their roles in agricultural biotechnology, including bio-pharming (Pew Initiative on Food and Biotechnology, 2004b).

A recent survey of legislative activity on biotechnology found that, in 2003, a total of 130 pieces of legislation were introduced in the states. Of those, 36 percent supported biotechnology, often as part of general economic development initiatives. Legislation aimed at supporting biotechnology proposed to start research and education initiatives; to spur economic and business development by providing loans and other assistance; and to offer tax incentives to biotechnology corporations and businesses. Legislation also addressed specific state concerns. For instance, Hawaiian legislators introduced bills meant to protect and capitalize on the state's biodiversity; legislators in northern plains states introduced bills addressing the potential market impacts of genetically engineered wheat. Colorado legislation was part of the trend in supporting biotechnology: One bill introduced during the 2003-2004 session of the Colorado General Assembly, and later signed into law, emphasized economic development by extending the activities of Colorado's Advanced Technology Fund to include the funding of research and technology transfer in biotechnology and other advanced technologies (Pew Initiative on Food and Biotechnology, 2004b).

Colorado stakeholders: insights, ideas and opinions

As part of "Bio-Pharming in Colorado: A Guide to Issues for Making Informed Choices," the Colorado Institute of Public Policy held four focus-group meetings in May 2004 (see Appendix A for a full summary of findings). The discussion groups gathered in agricultural communities, one in each quadrant of the state, and involved 56 state residents interested in and potentially affected by bio-pharming. Many of these stakeholders are community leaders in the state's agricultural regions; most had some knowledge of bio-pharming. Participants included conventional farmers, organic farmers, agricultural businesspeople, economic-development experts, cooperative extension agents, county commissioners, and members of interest and industry groups. Invitees were identified with help from Colorado State University Cooperative Extension directors and agents.

The community discussions lasted two hours each and generated insights, ideas and opinions from state residents who could be on the front lines of the technology's application in Colorado. Significantly, the discussions also generated many questions about bio-pharming; meeting participants said they want answers before they can help Colorado decision makers determine how to pursue bio-pharming.

Key findings:

- Issues related to gene flow and commingling – often referred to as safety issues – were a central theme of community discussions about bio-pharming.
    - Some focus-group participants were confident that risk-abatement requirements and regulatory oversight could prevent potential risks posed by bio-pharm gene flow and inadvertent commingling;
    - Many participants posed questions about potential risks and strategies to mitigate them;
    - Many participants voiced concern that bio-pharming in Colorado could negatively impact markets for Colorado crops regardless of success controlling gene flow and commingling, mainly because of public perceptions about crop biotechnology; and
    - Some participants were concerned about risks and skeptical of the effectiveness of control measures.
- Discussion participants said they want more information about bio-pharming, preferably based on independently conducted research. They said such information would:
    - Help state residents understand potential short-term and long-term risks and benefits, including those relevant to human health, the environment, and local and state economies;
    - Help state residents analyze risks and benefits;
    - Help people make decisions based on fact, rather than perceptions;
    - Help advance the technology and perfect the safeguards used in its application;
    - Help identify appropriate cultivation protocols, host plants, growing settings and regulations; and
    - Help build public confidence in bio-pharming.

- Participants universally agreed that economic development would most likely occur with Colorado bio-pharming through attraction and retention of crop cultivation, processing and related activity, all under appropriate safeguards.
    - Many participants said locally integrated bio-pharm cultivation and processing could boost Colorado's agricultural communities; and
    - Some participants doubted that drug companies would move operations to rural Colorado, and were skeptical about the potential for economic gain.

This paper was designed, in part, to answer questions from Colorado stakeholders, including those who took part in focus groups. The bio-pharming focus groups also began what could be fruitful bio-pharming policy discussions involving state residents and decision makers. As discussed elsewhere in this paper, stakeholder involvement could be central to decisions that are both scientifically and ethically sound. Stakeholders provide useful information and ideas to help determine how Colorado might derive the greatest benefits with fewest risks from bio-pharming.

Conclusion

Colorado is at a policy crossroads with bio-pharming. This paper addresses relevant policy issues – both potential benefits and potential risks – for consideration in bio-pharm decision-making. It explains why Colorado decision makers might want to consider both scientifically derived data and community values when forming policies about the technology and its application in the state. The paper offers frameworks to help guide decisions about whether to pursue bio-pharming in Colorado, and how to apply the technology in ways that could maximize its benefits and minimize its risks.

References

Alper, J. (2003). Hatching the golden egg: A new way to make drugs. *Science, 300*, 729-730.

Animal and Plant Health Inspection Service (APHIS) (2002). USDA investigates biotech company for possible permit violations. *News & Info, U.S. Department of Agriculture Animal and Plant Health Inspection Service*. Retrieved August 11, 2004, from http://www.aphis.usda.gov/lpa/news/2002/11/prodigene.html

APHIS (2003a). *USDA strengthens 2003 permit conditions for field testing genetically engineered plants*. Retrieved March 7, 2003, from http://www.aphis.usda.gov/lpa/news/2003/03/gepermits_brs.html

APHIS (2003b). *USDA to require permits for all industrial biotech plants*. Retrieved August 6, 2003, from http://www.aphis.usda.gov/lpa/news/2003/08/bioplants_brs.html

APHIS (2004a, January). *Updated guidance on bioengineered plants for producing pharmaceuticals or industrial products for applicants developing these plants for release*. Retrieved January 15, 2004, from http://www.aphis.usda.gov/brs/pharmaceutical.html

APHIS (2004b, September). Release permits for pharmaceuticals, industrials, value added proteins for human consumption, or for phytoremediation. *USDA Animal and Plant Health Inspection Service Biotechnology Regulatory Services*. Retrieved August 4, 2004, from http://www.aphis.usda.gov/brs/ph_permits.html

Ashford, N., Barrett, K., Bernstein, A., Costanza, R., Costner, P., Cranor, C., et al. (1998). Wingspread statement on the Precautionary Principle. *The Global Development Research Center – Urban Governance*. Retrieved August 3, 2004, from http://www.gdrc.org/u-gov/precaution-3.html

Associated Press (2002, May 28). Biotech industry squeezed by lack of "breweries." *San Diego Union-Tribune*. Retrieved April 7, 2004, from http://www.signonsandiego.com/news/science/20020527-1423-bioreactorshortage.html

Auge, K. (2003a, June 16). Colorado to field "biopharmed" corn; state OKs acres for disputed crop. *The Denver Post*, p. A1.

Auge, K. (2003b, June 19). Despite OK, no biopharm corn crop this year in Colorado. *The Denver Post*, p. B2.

Aylor, D.E., Schultes, N.P., and Shields, E.J. (2003). An aerobiological framework for assessing cross-pollination in maize. *Agricultural and Forest Meteorology, 119*, 111-129.

Bakker, H., Bardor, M., Molthoff, J.W., Gomord, V., Elbers, I., Stevens, L.H., et al. (2001). Galactose-extended glycans of antibodies produced by transgenic plants. *Proceedings of the National Academy of Sciences, 98*, 2899-2904.

Bartik, T. (1994). Jobs, productivity and local economic development: What implications does economic research have for the role of government? *National Tax Journal, 47*, 847-861.

Baucom, R.S., and Mauricio, R. (2004). Fitness costs and benefits of novel herbicide tolerance in a noxious weed. *Proceedings of the National Academy of Sciences, 101*, 13386-13390.

Becker, M. (2003, June 18). Meristem holds off; says it's too late to plant. *Sterling Journal-Advocate*.

Benbrook, C. (1999, January). *World food system challenges and opportunities: GMOs, biodiversity and lessons from America's heartland*. Paper presented at the World Food and Sustainable Agriculture Program, University of Illinois. Retrieved February 2, 2004, from http://www.pmac.net/IWFS.pdf

Biotechnology Industry Organization (2002). *Plant-made pharmaceuticals: Frequently asked questions*. Retrieved February 16, 2004, from http://www.bio.org/healthcare/pharmaceutical/pmp/factsheet2.asp

Biotechnology Industry Organization (2004). *Statement regarding plants that produce pharmaceutical and industrial products*. Retrieved July 29, 2004, from http://www.bio.org/healthcare/pharmaceutical/pmp/statement.asp

Birdsley-Jensen, C., and Poulsen, L.K. (1997). Hazards of unintentional/intentional introduction of allergens into foods. *Allergy, 52*, 1184-1186.

Boerboom, C. (2002). *Is there a risk of a GMO gene moving to weeds?* Retrieved April 14, 2004, from http://ipcm.wisc.edu/uw_weeds/extension/articles/GMOgenemove.htm

Brand, R. (2004, March 13). Feed corn, meet "pharma corn." *Rocky Mountain News*, p. C1.

Bruhn, C. (2003). Consumer attitudes toward biotechnology: Lessons for animal-related applications. *Journal of Animal Science, 81(E Suppl 2)*, E196-E200.

Byrne, P., Ward, S., and Harrington, J. (2003). *Transgenic crops: An introduction and resource guide*. Retrieved March 4, 2004, from http://www.colostate.edu/programs/lifesciences/TransgenicCrops/index.html

Canadian Food Inspection Service (2001). *Plant molecular farming discussion document*. Retrieved May 7, 2004, from http://www.inspection.gc.ca/english/plaveg/pbo/mf/mf_disde.shtml

Carman, D. (2003, October 3). Biopharming backer makes his point; then again … *The Denver Post*, p. B1.

Center for Science in the Public Interest (2002, December). *The future of pharming: Can it be done safely?* Panel discussion at National Press Club, Washington, D.C. Retrieved January 26, 2004, from http://www.cspinet.org/new/200212301.html

Colorado Agricultural Statistics Service (2003). *Colorado Agricultural Statistics*. Retrieved August 1, 2003, from http://www.nass.usda.gov/co/

Colorado Department of Agriculture (2003). *Colorado Department of Agriculture seeking input from public*. Retrieved November 24, 2003, from http://www.ag.state.co.us/biotech.html

Colorado Department of Agriculture (2004). *Evaluating experimental biotechnology permits for plant made industrial and pharmaceutical products in Colorado*. Retrieved November 24, 2003, from http://www.ag.state.co.us and http://www.ag.state.co.us/biotech.html

Conrad, U., and Fiedler, U. (1998). Compartment-specific accumulation of recombinant immunoglobulins in plant cells: An essential tool for antibody production and immunomodulation of physiological functions of pathogen activity. *Plant Molecular Biology, 38*,101-109.

Cornelius, C. (2002, May 19). Drought drains life from ag industry. *The Denver Post*, p. A1.

Crosby, L. (2003). Commercial production of transgenic crops genetically engineered to produce pharmaceuticals. *BioPharm International*, 60-67. Retrieved July 20, 2004, from http://www.biopharm-mag.com/biopharm/data/articlestandard/biopharm/172003/54511/article.pdf

Daniell, H. (2002). Molecular strategies for gene containment in transgenic crops. *Nature Biotechnology, 20*, 581-586.

Dechant, D. (2003). Drug corn and the meaning of a zero percent tolerance level. *CropChoice*. Retrieved August 3, 2004, from http://www.cropchoice.com/leadstry.asp?recid=1451

Dellinger, P. (2003, April 13). Bankrupt CropTech seeking investors. *The Roanoke (Va.) Times*, p. NRV3.

Derra, S. (2004). *Regents professor creates vaccines for developing countries*. Retrieved July 12, 2004, from http://www.asu.edu/asunews/faculty_students/regents_arntzen.htm

Dow Chemical Company (2004). *Dow to produce NOBEX peptide in plant-based system*. Retrieved March 19, 2004, from http://www.dow.com/dow_news/prodbus/2004/20040217a.htm

Drugs in crops – the unpalatable truth (2004). *Nature Biotechnology editorial, 22*,133.

Dry, L. (2002). The case for plant-made pharmaceuticals. *Biotechnology Industry Association News*. Retrieved March 19, 2004, from http://www.bio.org/healthcare/pharmaceutical/pmp/bionews200204.pdf

Duffy, M. (2001, December). *Who benefits from biotechnology?* Paper presented at the American Seed Trade Association meeting in Chicago, IL.

Elliott, V. (2004, July 13). GM crops may be grown for vaccines. *The Times of London*, p. 3C-2.

Ellstrand, N. (2001). When transgenes wander, should we worry? *Plant Physiology, 125*, 1543-1545.

Ellstrand, N. (2003a). Current knowledge of gene flow in plants: Implications for transgene flow. *Philosophical Transactions of the Royal Society of London, 358*, 1163-1170.

Ellstrand, N. (2003b). Going to "great lengths" to prevent the escape of genes that produce specialty chemicals. *Plant Physiology, 132*, 1770-1774.

Ellstrand, N., and Schierenbeck, K. (2000). Hybridization as a stimulus for the evolution of invasiveness in plants? *Proceedings of the National Academy of Sciences, 97*, 7043-7050.

Ellstrand, N.C., Prentice, H.C., and Hancock, J.F. (1999). Gene flow and introgression from domesticated plants into their wild relatives. *Annual Review of Ecology and Systematics, 30*, 539-563.

"Environmental Impact Statement: Introduction of genetically engineered organisms." *Federal Register* 69 (January 23, 2004): 3271-3272.

European Commission of the European Union (2002). *Life sciences and biotechnology – a strategy for Europe*. Retrieved August 18, 2004, from http://europa.eu.int/eur-lex/en/com/cnc/2002/com2002_0027en01.pdf

European Commission of the European Union (2004). *EU Commission authorizes import of canned GM sweet corn under new strict labeling conditions: Consumers can choose*. Retrieved August 13, 2004, from http://www.eurunion.org/news/press/2004/20040082.htm

Falk, W., and Lobao, L. (2003). Who benefits from economic restructuring? Lessons from the past, challenges for the future. In D.L. Brown and L.E. Swanson (Eds.) *Challenges for Rural America in the Twenty-First Century* (pp. 152-165). University Park, PA: The Pennsylvania State University Press.

Felsot, A. (2002). Pharm farming. *Agrichemical and Environmental News, 195*. Retrieved June 9, 2004, from http://aenews.wsu.edu

Flinn, J.E., and Zavon, J.A. (2004, August 1). Green plants as biofactories for drugs. *BioPharm International*. Retrieved September 29, 2004, from http://www.biopharminternational.com/biopharm/

Foutz, A. (2003, June 15). The future of farming; biopharm crops can be grown safely. *The Denver Post*, p. E1.

Fox, J. (2003). Puzzling industry response to ProdiGene fiasco. *Nature Biotechnology, 21*, 3-4.

Fraley, R.T., Rogers, S.G., Horsch, R.B., Eichholtz, D.A., Flick, J.S., Fink, C.L., et al. (1985). The SEV system: A new disarmed Ti plasmid vector system for plant transformation. *Bio/technology, 3*, 629-635.

Freese, B. (2002). *Manufacturing drugs and chemicals in crops: Biopharming poses new threats to consumers, farmers, food companies and the environment*. Retrieved March 11, 2004, from http://www.gefoodalert.org/pages/home.cfm

French company gets OK to plant biotech corn. (2003, June 5). *Associated Press*, Denver.

The Gallup Poll. (2001). *Biotech food remains fairly obscure to most Americans*. Retrieved March 17, 2004, from http://www.gallup.com

Gepts, P. (2002). A comparison between crop domestication, classical plant breeding and genetic engineering. *Crop Science, 42*, 1780-1790.

Green, M. (2003, June 5). Biopharm corn gets OK from state. *Sterling Journal-Advocate*.

Guan, X., Stege, J., Kim, M., Dahmani, Z., Fan, N., and Heifetz, P., et al. (2002). Heritable endogenous gene regulation in plants with designed polydactyl zinc finger transcription factors. *Proceedings of the National Academy of Sciences, 99*, 13296-13301.

Hamilton, N.D. (2003, April). *Forced feeding: Inventorying new legal issues in the biotechnology policy debate*. Paper presented at Biodiversity, Biotechnology and the Protection of Traditional Knowledge conference at Washington University, St. Louis. Retrieved August 3, 2004, from http://law.wustl.edu/centeris/Confpapers/

Hanrahan, C., Becker, G.S., and Jurenas, R. (2002). Agricultural trade issues in the 107th Congress. *Congressional Research Service, issue brief for Congress no. IB10077*. Retrieved August 11, 2004, from http://www.ncseonline.org/NLE/CRSreports/03Feb/IB10077.pdf

Hibbs, E. (2003, September 29). Biopharmers urged to consider Colorado plant. *Sterling Journal-Advocate*.

Hoban, T. (1998). Trends in consumer attitudes about agricultural biotechnology. *AgBioForum, 1*, 3-7.

Hoban, T., and Kendall, P. (1993). *Consumer attitudes about food biotechnology* (USDA special project No. 01-EXCA-3-0155). Raleigh, N.C.: North Carolina Cooperative Extension Service.

Huang, S. (2000). Practical problems of post-genomic techniques. *Nature Biotechnology, 18*, 471-472.

INRA (Europe) (2002). *The Europeans and biotechnology*. Retrieved March 4, 2004, from http://europa.eu.int/comm/public_opinion/archives/eb/ebs_134_en.pdf

Iowa State University (2003). *New institute to evaluate genetically modified organisms*. Retrieved January 28, 2004, from http://www.ag.iastate.edu/aginfo/news/2003releases/bigmap.html

Jaffe, G. (2004, June). *Sowing secrecy: The biotech industry, USDA and America's secret pharm belt*. Retrieved January 26, 2004, from http://www.cspinet.org

Jones, M.D., and Brooks, J.S. (1950). Effectiveness of distance and border rows in preventing outcrossing in corn. *Oklahoma Agricultural Experiment Station, bulletin no. T-38*.

Kaiser, M. (2002). Introduction to the special issue on Precautionary Principle. *Journal of Agricultural and Environmental Ethics, 15*, 1-5.

Koo, J.C., Asurmendi, S., Bick, J., Woodford-Thomas, T., and Beachy, R.N. (2004). Ecdysone agonist-inducible expression of a coat protein gene from tobacco mosaic virus confers viral resistance in transgenic Arabidopsis. *The Plant Journal, 37*, 439-448.

Kostandini, G., Mills, B., and Norton, G. (2004, August). *Potential impacts of pharmaceutical uses of transgenic tobacco: The case of human serum albumin*. Paper presented at the American Agricultural Economics Association annual meeting in Denver, CO. Retrieved August 12, 2004, from http://agecon.lib.umn.edu/cgi-bin/pdf_view.pl?paperid=14293&ftype=.pdf

Large Scale Biology Corporation (2004a). *Large Scale Biology Corporation and Planet Biotechnology Inc. announce biomanufacturing agreement*. Retrieved July 16, 2004, from http://biz.yahoo.com/iw/040715/069935.html

Large Scale Biology Corporation (2004b). *LSBC announces production of interferon alpha*. Retrieved October 1, 2004, from http://www.lsbc.com/

Lemaux, P. (2001). *The what and how of plant biotechnology*. Retrieved June 7, 2004, from http://ucbiotech.org/resources/

Luther, V., and Wall, M. (1998). *Clues to rural community survival*. Retrieved July 12, 2004, from http://www.heartlandcenter.info/

Mayfield, S.P., Franklin, S.E., and Lerner, R.A. (2003). Expression and assembly of a fully active antibody in algae. *Proceedings of the National Academy of Sciences, 100*, 438-442.

McCullum, C., Benbrook, C., Knowles, L., Roberts, S., and Schryver, T. (2003). Application of modern biotechnology to food and agriculture: Food systems perspective. *Journal of Nutrition Education Behavior, 35*, 319-332.

McGraw, L. (2001). Keeping transgenic pollen in its place. *Agricultural Research Service, U.S. Department of Agriculture.* Retrieved August 4, 2004, from http://www.ars.usda.gov/is/AR/archive/oct01/pollen1001.htm

Metcalfe, D.D. (2003). What are the issues in addressing the allergenic potential of genetically modified foods? *Environmental Health Perspectives, 111*, 1110-1113.

Mison, D. (2004, April). *Production of recombinant proteins in transgenic corn: Overcoming challenges of technology and safety assessment*. Talk during Risk Assessment Symposium: Corn-Produced Pharmaceuticals and Industrials, Biosafety Institute for Genetically Modified Agricultural Products, Iowa State University, Ames, IA. Retrieved July 11, 2004, from http://www.bigmap.iastate.edu/

Mison, D., and Curling, J. (2000). The industrial production costs of recombinant therapeutic proteins expressed in transgenic corn. *Biopharm – The Applied Technologies of Biopharmaceutical Development, 13*, 48-54.

Montana State University (2004). *Pharmaceutical crops: promise or peril?* Retrieved June 8, 2004, from http://www.montana.edu/commserv/csnews/nwview.php?article=1467

Morrison, L.A., Riera-Lizarazu, O., Cremieux, L., and Mallory-Smith, C.A. (2002). Jointed goatgrass (*Aegilops cylindrica* host) x wheat (*Triticum aestivum* L.) hybrids: Hybridization dynamics in Oregon wheat fields. *Crop Science, 42*, 183-1872.

National Governors Association (2003). *Innovative state policy options to promote rural economic development*. Retrieved July 12, 2004, from http://www.nga.org/cda/files/0203RURALDEV.pdf

National Research Council (2000). *Genetically modified pest-protected plants: Science and regulation*. Washington, D.C.: The National Academies Press.

National Research Council (2002). *Environmental effects of transgenic plants: The scope and adequacy of regulation*. Washington, D.C.: The National Academies Press.

National Research Council (2004a). *Biological confinement of genetically engineered organisms*. Washington, D.C.: The National Academies Press.

National Research Council (2004b). *Safety of genetically engineered foods: Approaches to assessing unintended health effects*. Washington, D.C.: The National Academies Press.

Nestmann, E., Copeland, T., and Hlywka, J. (2002). The regulatory and science-based safety evaluation of genetically modified food crops: A USA perspective. In K. Atherton (Ed.), *Genetically Modified Crops: Assessing Safety* (pp. 1-44). London: Taylor & Francis.

Nordlee, J.A., Taylor, S.L., Townsend, J.A., and Thomas, L.A. (1996). Identification of a brazil nut allergen in transgenic soybeans. *The New England Journal of Medicine, 334*, 688-692.

Ohlrogge, J., and Chrispeels, M.J. (2003). Plants as chemical and pharmaceutical factories. In M.J. Chrispeels and D.E. Sadava (Eds.), *Plants, genes and biotechnology* (pp. 500-527). Sudbury, MA: Jones and Bartlett Publishers.

Ordiz, M.I., Barbas, C.F., III, and Beachy, R.N. (2002). Regulation of transgene expression in plants with polydactyl zinc finger transcription factors. *Proceedings of the National Academy of Sciences, 99*, 13290-13295

Organisation for Economic Co-operation and Development (2004). *Biotechnology for sustainable growth and development*. Retrieved August 24, 2004, from http://www.oecd.org/dataoecd/60/63/23536372.pdf

Peterson, R., and Arntzen, C. (2004). On risk and plant-based biopharmaceuticals. *Trends in Biotechnology, 22*, 64-66.

Pew Initiative on Food and Biotechnology (2002a). *Environmental savior or saboteur? Debating the impacts of genetic engineering*. Retrieved May 5, 2004, from http://pewagbiotech.org/events/0204/

Pew Initiative on Food and Biotechnology (2002b, July). Pharming the field: A look at the benefits and the risks of bioengineering plants to produce pharmaceuticals. Proceedings from conference co-sponsored by the U.S. Food and Drug Administration and the Cooperative State Research, Education and Extension Service of the U.S. Department of Agriculture. Retrieved February 9, 2004, from http://pewagbiotech.org/events/0717/

Pew Initiative on Food and Biotechnology (2002c, July). On the pharm: GM plants and the future of medicine. *AgBiotech Buzz, 2*. Retrieved March 8, 2004, from http://pewagbiotech.org/buzz/index.php3?IssueID=14

Pew Initiative on Food and Biotechnology (2003b). *Have transgenes, will travel: Issues raised by gene flow from genetically engineered crops*. Retrieved May 20, 2004, from http://pewagbiotech.org/resources/issuebriefs/geneflow.pdf

Pew Initiative on Food and Biotechnology (2004a). *Issues in the regulation of genetically engineered plants and animals*. Retrieved May 5, 2004, from http://pewagbiotech.org/research/regulation/

Pew Initiative on Food and Biotechnology (2004b). *2003 legislative activity related to agricultural biotechnology*. Retrieved July 12, 2004, from http://pewagbiotech.org/resources/factsheets/legislation/factsheet.php

Phillips, M. (2004, April). *Plant-made pharmaceutical confinement systems*. Talk during Risk Assessment Symposium: Corn-Produced Pharmaceuticals and Industrials, Biosafety Institute for Genetically Modified Agricultural Products, Iowa State University, Ames, IA. Retrieved July 11, 2004, from http://www.bigmap.iastate.edu/

Polancic, J. (2003). *About biotech, DNA primer: An introduction to DNA and disease detection*. Access Excellence at the National Health Museum, About Biotech series. Retrieved July 6, 2004, from http://www.accessexcellence.org/

Pollack, A. (2003, October 16). Monsanto overhauling business. *The New York Times*.

Pollack, A. (2004, September 21). Genes from engineered grass spread for miles, study finds. *The New York Times*.

Porter, A. (2004, January 27). Bio-engineered crops could face new rules. *The (Grand Junction) Daily Sentinel*.

Probert, S. (2004, July 13). GM trials to change life down on the pharm. *The Birmingham (UK) Post*.

ProdiGene fined for contaminating soybeans with genetically engineered corn (2003). *Biotechnology Law Report, 22*, 114.

Redick, T.P. (2003). Biopharming, biosafety and billion dollar debacles: Preventing liability for biotech crops. *Drake Journal of Agricultural Law, 8*, 115.

Researchers developing risk analysis tool for biopharm crop production. (2003, April 16). *Biotech Week*, p. 49.

Rieger, M.A., Lamond, M., Preston, C., Powles, S.B., and Roush, T.R. (2002). Pollen-mediated movement of herbicide resistance between commercial canola fields. *Science, 296*, 2386-2388.

Ritala, A., Nuutila, A.M., Aikasalo, V., Kauppinen, V., and Tammisola, J. (2002). Measuring gene flow in the cultivation of transgenic barley. *Crop Science, 42*, 278-285.

Rogers, K. (2003). *The potential of plant-made pharmaceuticals*. Retrieved July 16, 2004, from http://plantpharma.org/ials/index.php?id=1

Rollin, B.E. (1995a). There are certain things humans were not meant to do. *The Frankenstein syndrome: Ethical and social issues in the genetic engineering of animals* (pp. 1-66). Cambridge, NY: Cambridge University Press.

Rollin, B.E. (1995b). Rampaging monsters. *The Frankenstein syndrome: Ethical and social issues in the genetic engineering of animals* (pp. 67-134). Cambridge, NY: Cambridge University Press.

Rollin, B.E. (1996a). Ideology, "value-free science" and animal welfare. *ACTA Agriculturae Scandinavica Section A-Animal Science Suppl. 27, 5-10*.

Rollin, B.E. (1996b). Bad ethics, good ethics and the genetic engineering of animals in agriculture. *Journal of Animal Science, 74*, 535-541.

Rollin, B.E. (1997). Send in the clones … don't bother, they're here! *Journal of Agricultural and Environmental Ethics, 10*, 25-40.

Roosevelt, M. (2003, May 26). Cures on the cob. *Time*. Retrieved August 11, 2004, from http://www.time.com/time/

Schmitz, T.G., Schmitz, A., and Moss, C.B. (2004). Did StarLink reduce import demand for corn? *Journal of Agricultural & Food Industrial Organization, 2*, article 6.

Scott, A. (2003, December 11). No lifting of Euro GM ban, yet. *The Scientist*. Retrieved February 16, 2004, from http://www.biomedcentral.com/news/20031211/03

Segal, D.J., and Barbas, C.F., III (2001). Custom DNA-binding proteins come of age: Polydactyl zinc-finger proteins. *Current Opinion in Biotechnology, 12*, 632-637.

Segal, D.J., Dreier, B., Beerli, R.R., and Barbas, C.F., III (1999). Toward controlling gene expression at will: Selection and design of zinc finger domains recognizing each of the 5'-GNN-3' DNA target sequences. *Proceedings of the National Academy of Sciences, 96*, 2758-2763.

Segarra, A.E., and Rawson, J.M. (2001). StarLink™ corn controversy: Background. *Congressional Research Service, report for Congress no. RS20732*. Retrieved August 2, 2004, from http://www.ncseonline.org/nle/crsreports/agriculture/ag-101.cfm

Shanahan, J., Scheufele, D., and Lee, E. (2001). The polls – trends: Attitudes about agricultural biotechnology and genetically modified organisms. *Public Opinion Quarterly, 65*, 267-281.

Simon, B. (2004, May 22). Monsanto wins patent case on plant genes. *The New York Times*.

Sheridan, M. (2004, February 17). Dow Chem, NOBEX in pact for proprietary peptide production. *Chemical News & Intelligence*.

Snow, A.A. (2002). Transgenic crops – why gene flow matters. *Nature Biotechnology, 20*, 542.

Snow, A.A., and Palma, P.M. (1997). Commercialization of transgenic plants: Potential ecological risks. *Bioscience, 47*, 86-96.

Snow, A.A., Pilson, D., Rieseberg, L.H., Paulsen, M.J., Pleskac, N., Reagon, M.R., et al. (2003). A Bt transgene reduces herbivory and enhances fecundity in wild sunflowers. *Ecological Applications, 13*, 279-286.

Stege, J.T., Guan, X., Ho, T., Beachy, R.N., and Barbas, C.F., III (2002). Controlling gene expression in plants using synthetic zinc finger transcription factors. *The Plant Journal, 32*, 1077-1086.

Stewart, K. (2003, March 29). CropTech Corp. files for Chapter 11; company's chief financial officer says firm has stopped operating. *The Roanoke (Va.) Times*.

Suhr, J. (2003, October 15) Monsanto posts $188 million loss in 4Q. *Associated Press Online, financial news*.

Taylor, M., and Tick, J. (2001). The StarLink case: issues for the future. *Pew Initiative on Food and Biotechnology issue brief*. Retrieved July 30, 2004, from http://pewagbiotech.org/resources/issuebriefs/starlink/

Taylor, M., and Tick, J. (2003). Post-market oversight of biotech foods: Is the system prepared? *Pew Initiative on Food and Biotechnology report*. Retrieved January 27, 2004, from http://pewagbiotech.org/research/postmarket/

U.S. Department of Agriculture (2004). USDA announces first steps to update biotechnology regulations. *Newsroom, U.S. Department of Agriculture*. Retrieved February 5, 2004, from http://www.usda.gov/Newsroom/0033.04.html

U.S. Food and Drug Administration (2002, September). Guidance for industry: Drugs, biologics, and medical devices derived from bioengineered plants for use in humans and animals. *U.S. Department of Health and Human Services*. Retrieved August 2, 2004, from http://www.fda.gov/cber/gdlns/bioplant.pdf

University of California (2001). What kinds of new GM plants will come to the fields in the future? *University of California Division of Agricultural and Natural Resources Statewide Biotechnology Workgroup issues brief*. Retrieved July 13, 2004, from http://ucbiotech.org

Walsh, G. (2000). Biopharmaceutical benchmarks. *Nature Biotechnology, 18*, 831-833.

Walsh, J.T., and Redick, T.P. (2003, January). Managing agricultural risks in biopharming: The role of injunctions. *American Bar Association Agricultural Management Committee Newsletter*. Retrieved August 3, 2004, from http://www.abanet.org/environ/committees/agricult/newsletter/jan03/biopharming.html

Walz, E. (2004). Fourth national organic farmers' survey: Sustaining organic farms in a changing organic marketplace. *Organic Farming Research Foundation*. Retrieved August 6, 2004, from http://www.ofrf.org/publications/survey/Final.Results.Fourth.NOF.Survey.FastView.pdf

Watrud, L.S., Lee, E.H., Fairbrother, A., Burdick, C., Reichman, J.R., and Bollman, M., et al. (2004). Evidence for landscape-level, pollen-mediated gene flow from genetically modified creeping bentgrass with CP4 EPSPS as a marker. *Proceedings of the National Academy of Sciences, 101*, 14533-14538.

Weiler, S. (2000). Information and market failure in local economic development: A new role for universities? *Economic Development Quarterly, 14*, 194-203.

Weiss, R. (2004, May 21). Court rules against farmer in biotech dispute. *Washington Post*.

Whitton, J., Wolf, D.E., Arias, D.M., Snow, A.A., and Rieseberg, L.H. (1997). The persistence of cultivar alleles in wild populations of sunflowers five generations after hybridization. *Theoretical and Applied Genetics, 95*, 33-40.

Witte, G. (2004, January 23). Rules on biotech crops to be revised. *Washington Post*, p. A2.

Wolt, J. (2004, April). *Risks of confined field production of corn expressing pharmaceutically active compounds*. Talk during Risk Assessment Symposium: Corn-Produced Pharmaceuticals and Industrials, Biosafety Institute for Genetically Modified Agricultural Products, Iowa State University, Ames, IA. Retrieved July 11, 2004, from http://www.bigmap.iastate.edu/ and http://129.186.108.103

Zinnen, T. (2002). Nebraska crop contamination issue briefing. *Biotechnology Policy & Outreach, University of Wisconsin-Madison*. Retrieved August 16, 2004, from http://www.biotech.wisc.edu/Education/prodigene.html

Zitner, A (2001, June 4). Fields of gene factories: For the bioengineering revolution, the next big step may be plants that can make industrial chemicals and drugs. Why build expensive facilities when you can just grow what you need? *Los Angeles Times*, p. A1.

APPENDIX A

Bio-pharming in Colorado: findings from community focus groups

Top issues identified by participants*

ISSUE	Delta	Durango	Sterling	Walsh	TOTAL
SAFETY CONCERNS					**39**
Containment	8	5	2	2	17
For growers	3		1	4	8
For consumers	5		1		6
Security: facilities and processing			3		3
Protocols will be breached	1			1	2
In transporting grain			2		2
For water/land	1				1
KNOWLEDGE					**35**
Communities/growers lack sufficient information to make informed decisions	5		5		10
Need to educate public	1		1	5	7
Passionate opinions despite level of knowledge, many different opinions	3	1	2	1	7
Misconceptions and fear abound	1	4			5
No one knows consequences ("what if" scenarios)	1	1		2	4
Need more public discussion	1			1	2
ECONOMIC BENEFITS					**34**
Want for local community: need full production process in community	11	2	7	3	23
Has real potential – now and future	1	2	3	2	8
Pharmaceutical companies will gain most		2			2
Can state afford it?		1			1
REGULATORY ISSUES					**18**
Need strict regulations		2	1	6	9
Growers need to know more		2		2	4
Who's in charge?		1	1		2
Local/state should lead				1	1
Who pays for enforcement?		1			1
How enforced?		1			1
RISK ASSESSMENT					**16**
Need fact-based risk assessments	2	2	1	3	8
Farmers need more information	2		1	1	4
Risks are high		1		1	2
Need to take calculated risk, based on risk-benefit ratio		2			2
RESEARCH					**12**
Need more before open-air bio-pharm crop cultivation, and findings should be provided to state residents	2	3		2	7
Independent/unbiased research needed, not just industry-driven	1			4	5
LEGAL					**7**
Who is liable?			5	2	7
OTHER					**5**
Medical benefits are high			1	1	2
Need to quantify all types				1	1
How to attract companies?			1		1
Can Native American tribes benefit?		1			1
Proceed with caution				1	

* At the end of each focus group, participants wrote down what they considered to be the three most important issues raised during discussion. This table displays the issues participants identified. Numbers are presented in descending order of frequency in broad categories and subcategories.

Bio-pharming focus group in Delta, Colo., May 10, 2004

17 participants, primarily from Delta, Mesa and Montrose counties on the state's Western Slope; 13 men, 4 women.

- 6 conventional farmers
- 3 organic farmers
- 2 economic-development experts
- 1 county commissioner
- 1 cooperative extension employee
- 1 environmentalist
- 1 water manager
- 1 agricultural business person
- 1 employee, federal agency

(Participant quotations come from a meeting transcript and are provided to illustrate themes that emerged during the two-hour community discussion. For confidentiality, participants are identified by number instead of name.)

Summary:

- All participants had pointed questions about bio-pharming safety and economics. Much of the discussion centered on balance of risks and benefits, with participants questioning whether possible benefits are worth possible risks. Attendees agreed they want unbiased, research-based answers before they can decide whether they want to pursue bio-pharming on the Western Slope, and under what conditions. Growers, particularly conventional growers, were eager to explore options that might make farming more profitable. Organic growers were skeptical of bio-pharming's economic promise and of the effectiveness of mechanisms used to control gene flow and commingling. Economic-development specialists noted that a financial boost for one industry sector should not devalue another. Attendees agreed that crop cultivation alone will not likely yield widespread economic benefit.

Main themes, in order of frequency mentioned:

- Most meeting participants, regardless of background, identified potential contamination issues as the main focus of their questions or concerns about bio-pharming. All agreed that an incident involving unintentional gene flow or commingling could have a serious, even devastating, impact on crop markets. Participants who saw promise in bio-pharming said they want proven safeguards before pursuing the technology; those skeptical of bio-pharming's promise said possible contamination risks were a central reason. Meeting participants agreed that bio-pharm contamination issues must be fully addressed for the technology to move ahead in Colorado.
    - (18) Conventional farmer: "I grow about 250 acres of sweet corn for the fresh market. If it was contaminated, it would be indefensible. I don't think anybody sitting around this table is going to agree to grow something until we are sure that it's not going to cause contamination problems. It would be a total disaster if we couldn't sell our crops after we raised them, after we put about $600 an acre into that crop to get it to the point of harvest."
    - (10) Conventional farmer: "If there's some economic benefit to what I do, and I could say that I had a chance to help solve the risk of cancer or diabetes or something like that, I would be the first in line to help. But I would need to do it safe."

- (1) Water manager: "I have some questions about the cross-pollination of these genetically engineered crops. If it gets into the water, can it move into downstream deliveries that we might make? We have to make sure it's safe for the community we serve."
- (4) Environmentalist: "I'm worried about the contamination of food and feed crops with the genes that would come from bio-pharm crops."
- (12) Conventional farmer: "I don't see this as two sides here. I have farmed all my life, and I don't care if you farm organically or you farm conventionally, it's damned hard work. … We have millions of dollars invested in these farms, and the last damn thing anybody wants to do is screw them up."

- Meeting participants expressed frustration over lack of reliable information about an agricultural biotechnology that already has been introduced in the state and could affect them. Attendees said they want unbiased, research-based information about bio-pharming and its potential impacts on their community and their markets.
  - (2) Agricultural business person: "Is there someone who does know the answers to all these questions? Is there someone somewhere who does know the answers? Is there? We kind of need to talk."
  - (11) County commissioner: "You know how public opinion is – if it's really strong one way or another, that's really important. But I think what you can see from this group is that they want answers, want to make educated decisions, not just to dwell on who's for it or against it."
  - (7) Organic farmer: "One has to rely on sound research done by our state universities. You can't make regulations and guidelines unless you have the sound evidence of what is happening."
- Conventional growers and representatives of some other stakeholder groups indicated that they are inclined to trust the effectiveness of cultivation protocols if those cultivation safeguards have been tested and an appropriate regulatory structure is established prior to planting. These farmers said they think risk-abatement measures can be successfully enforced through contracts and regulations. Some meeting participants said they think fears of bio-pharming, even if not fact-based, are an obstacle.
  - (3) Conventional farmer: "Several of us were at a meeting where they gave all the research and how they expected to grow it. … I was convinced that with the isolation and the guidelines, it would be completely safe."
  - (15) Federal agency employee: "I think there's such a huge fear factor. Every regulatory agency in the world could say it's safe and there is a polarity there between this group that says, yes, it's OK, and this group that will never be convinced. And that group is not small. That group over here that says this is not good is not small. We may think it is, but I don't believe that. I think there's a tremendous fear factor today. … And I think it has the ability to be a tremendous elephant to the ag industry."
- While seeking answers to questions about safety, conventional growers also generally viewed bio-pharming as a possible boost for agriculture. They generally described Colorado's climactic conditions, and potential to geographically isolate bio-pharm crops, as an asset for the emerging technology.
  - (17) Conventional farmer: "I'm interested in the ability to make a living with some different crops than we have in the area, something that the margins are a little better on."
  - (12) Conventional farmer: "There's no question that if you want to keep agriculture, you've got to let them make money. That's the bottom line. Whether this is the crop, I don't know."

- (8) Conventional farmer: "Colorado is very isolated. Our valley, of course, isn't too isolated but we've got pockets that are isolated completely. On the Eastern Plains, you can drive for 4 or 5 miles and it's just grassland with a couple of pivots. And that's the reason they're coming from Iowa out to here is because we are isolated."
- (2) Agricultural business person: "I think we're all in favor of more viable ag alternatives, I certainly am. I think we're all in favor of producing quality products in our area; I think we pride ourselves on that. But I've still got questions."

- All attendees agreed that bio-pharm crop cultivation alone is unlikely to yield widespread economic benefit in Colorado. Organic growers voiced the most skepticism about economic promises, generally doubting bio-pharming's future viability and the potential for biotech firms to build processing plants in the state.
  - (12) Conventional farmer: "It probably would be based on very limited acreage, more than likely, and if you look at it from that standpoint, I'm not sure what the economic value would be to the community."
  - (6) Organic farmer: "I think the only way it would be beneficial to the community is if there were a facility that actually processed it here, and that created jobs eventually – so that more people benefited than that one 50-acre plot or whoever owns that plot."
  - (7) Organic farmer: "I think that them coming in with a lot of capital in an out-of-the-way area is not real probable."
- Participants representing all stakeholder groups questioned how much risk and how much benefit bio-pharming could present. They wondered if benefits justify the risks. Differing views on risk emerged. Organic growers voiced concern that the mere presence of bio-pharming in the area or state could undermine their markets.
  - (14) Economic-development expert: "One or two growers in the area are not going to put enough money back into the community for the whole community to realize a great benefit. There may be one or two growers that are doing well and are able to buy new equipment and some of those things get turned over. But on the scale that it would take in order to really create a large impact in the community, it would have to be thousands and thousands and thousands of acres for everyone to really benefit from it. Then you start getting into the other issues of cross-contamination against our organic growers who are working in an isolated area, and they've worked very hard to build up the value of their crops. So it's a real double-edged sword."
  - (13) Economic-development expert: "This, on the surface, sounds like a good idea. But if it damages other crops that are grown in the area and it's just a select few that can grow it, then I think that's something we'd have to know. It could defeat the purpose."
  - (5) Organic farmer: "If Colorado becomes known as a bio-pharm state, there are going to be a lot of organic markets that are closed to us. We do have quite a few people who do a lot of export markets, and any of the export markets are not GMO friendly."
  - (9) Cooperative extension employee: "If anyone expects anything that man has developed to be 100 percent safe, you're kidding yourself. You're absolutely kidding yourself. How many people do we kill in automobiles every day? Nothing that man has produced is 100 percent safe, and it never will be."
- Also during the meeting:
  - Some participants voiced concern over information about bio-pharming experiments being withheld from the public on the grounds that it is proprietary, or confidential business information.

- Attendees generally agreed that some bio-pharm products would be more acceptable than others based on the risks presented. They characterized lipase, for instance, as being on the more-acceptable end of the spectrum, and some hormones on the less-acceptable end of the spectrum.
- Some participants raised questions about potential liability issues and who bears the costs of gene-confinement failures.
- Some attendees voiced concern over the potential for sabotage of bio-pharm crops.

Bio-pharming focus group in Durango, Colo., May 17, 2004

13 participants from southwestern Colorado; 7 women, 6 men.

- 3 organic farmers
- 2 economic-development specialists
- 2 extension agents
- 2 organic ranchers
- 1 community activist
- 1 county commissioner
- 1 nurse
- 1 retired scientist

(Participant quotations come from a meeting transcript and are provided to illustrate themes that emerged during the two-hour community discussion. For confidentiality, participants are identified by number instead of name.)

Summary:

- Participants asked multiple questions about potential immediate and secondary impacts posed by unintentional bio-pharm gene flow and commingling. Attendees concerned about possible gene-confinement failures worried about potential health impacts, environmental impacts and impacts on agricultural markets, especially markets for organic products. Stakeholders spent much of the meeting discussing risk-benefit apportionment – that is, who reaps the benefits of bio-pharming and who bears the risks; much of this discussion focused on whether potential benefits justify potential risks for Colorado communities and niche markets. All attendees said they want more reliable, research-based information about bio-pharming. Some stakeholders voiced deep suspicion about a technology they viewed as being driven by the profit motives of pharmaceutical companies; others identified important potential benefits for human health and Colorado agriculture. Discussion led participants to advocate bio-pharm development only in contained production systems, namely greenhouses.

Main themes, in order of frequency mentioned:

- All meeting participants said they have questions about issues related to gene flow and commingling, particularly as they relate to markets for organic products. Organic growers said bio-pharm crops grown anywhere in the state might hinder their markets because of negative public perceptions about genetically modified organisms. Some stakeholders said they want to know more about short-term and long-term environmental impacts of bio-pharming. While some attendees said they want science-driven safeguards, others indicated that they distrust the effectiveness of any safeguard with bio-pharm crops grown in open fields. Some at the meeting said they think profit motives cause drug companies, decision makers, regulators, researchers and other stakeholders to overlook or discount possible contamination risks.
    - (1) Organic farmer: "The issue paramount in my mind is the concern about bio-pharming impacts on marketing efforts, especially organic producers. … Meristem got approved last year, and I doubt we had much public input into that. There's irreversibility to some of this that we're talking about – not only on the environmental side, but also in the market. If Europe hears that Colorado is embracing bio-pharming, they could easily avoid us as a state, especially in the organic field. And that's a huge risk."
    - (11) Organic farmer: "We don't know the long term impacts of this technology, period. You can't call it back, and that's what's scary to me."

- (12) Organic rancher: "I think profit motive causes people not to look at all the consequences of the things that they are doing. … We keep saying that these things are not supposed to get into the food chain. Well, who's to say that they won't?"
- (8) Community activist: "I don't think any amount of protocols or regulation will keep it out of the system."

- Participants discussed who might benefit from bio-pharming, and who might bear risks, including potential liabilities. All advocated thorough risk-benefit analysis before the state and its communities pursue bio-pharming. Some at the meeting said biotechnology companies will benefit most from bio-pharming. Participants had differing philosophies about risk, ranging from concern about genetically engineered products to the belief that "there's a risk in everything," as a retired scientist put it.
  - (7) County commissioner: "It is a risk-benefit ratio. In my mind, if bio-pharming were to be of such benefit that it saves human lives or made the quality of life better, then I would be willing to have some risks associated."
  - (11) Organic farmer: "We don't know what the tradeoff is, that's my argument."
  - (6) Nurse: "The pharmaceutical industries are very powerful, very wealthy and very unethical in my view. … They have a huge profit motive here, and I think we need to be clearly aware that's why the pharmaceutical industry would be looking at La Plata County, or any place else for us to grow their materials. It's about their profit. And they don't always have a person's best interests at heart."
  - (12) Organic rancher: "It's my experience … that we don't think through many of our great leaps and look at the consequences. We just jump. We look at all the benefits and we don't think through the possible risks. We don't study them sufficiently, and we don't give enough time."
- Participants were united in their call for more unbiased and reliable research into bio-pharming and its potential impacts – so that any risks taken would be calculated risks. They said such research should drive risk-mitigation strategies and should be provided to the public so that Colorado residents and stakeholders have science-based answers to their questions about the technology. Some attendees raised technical questions: They wanted to know, for instance, how proteins are extracted, how plant material is destroyed after pharmaceutical processing, whether spontaneous hybrids potentially created from inadvertent bio-pharm gene flow could exhibit invasive characteristics, and whether proteins could leach from escaped seeds and cause problems.
  - (2) Organic rancher: "When you are ignorant of something, you have to become educated. But who's going to educate me, and what is their motive, is what makes me fearful."
  - (7) County commissioner: "I think research would be one step that would reassure us – if you did the research that it doesn't cross-contaminate other crops, or to show whatever else it is that people are concerned about. Do the research, and see if those fears are true or not."
  - (7.5) Extension agent: "Is there documented evidence or proof that this process has caused harm? Documented? … If we're talking about legislating, how do you legislate something that you don't know exactly what it will do? Really what you are talking about is legislating the unknown, to a degree."
- Some participants said they were confident that research-driven risk-abatement strategies, when properly enforced, could ensure bio-pharming safety and would allow Colorado and society to realize benefits from the technology. Attendees expressing this opinion said unfounded fears

could prevent benefits. A participant with diabetes said firsthand experience has shown that scientific advances, with proper safeguards, have the power to greatly help humankind and improve quality of life.

  - (4) Retired scientist: "There are at least 30 methods [described in a National Research Council report] of biological containment that can be put into the product or the seeds so that contamination doesn't occur."
  - (5) Economic-development specialist: "I think there is a difference between problems with any science in the present and its potential. We should not rule anything out because something could happen. I mean, I am not a fan of nuclear energy, but you don't want to say it is not a good science because we have had problems worldwide with nuclear energy. I hope that we don't let our fears keep us from developing something that could be of great benefit, or not. Let's not assume it's an evil industry, because the potential could be incredible."
  - (3) Economic-development specialist: "There's a place for research and discovery, and it can be handled in an appropriate manner and probably lead to some very beneficial sorts of things for humankind. I don't think that organic farming or traditional farming or bio-pharming have to be mutually exclusive. I think all of those things have their roles and can co-exist if done properly. … I look at a lot of things that people have probably been skeptical about for generations, and as time goes on there are clear and distinct benefits that come out of research that could have been squelched right on the spot."

- Most participants, regardless of background, agreed that enclosed cultivation settings, namely greenhouses, could provide important controls over experimental bio-pharming efforts. Growing bio-pharm crops in greenhouses, at least initially, would help build reliable data about the technology while also building public confidence, many participants agreed. The following exchange illustrates the point:
  - (7.5) Extension agent: "A properly constructed greenhouse with contamination controls can be very effective. It can have positive airflow that's going through, so that anytime the door opens, it immediately sucks it back in, through double-locking chambers."
  - (11) Organic farmer: "That's where I contend the research be done."
  - (3) Economic-development specialist: "I wouldn't disagree with that."
- Some participants foresaw little economic benefit for Colorado farmers and communities from bio-pharming, particularly under strict regulatory requirements and in light of industry controls over patented technology that is considered intellectual property.
  - (9) Extension agent: "Economic impact would probably be limited. In my community, most of the farmers and ranchers are somewhat averse to regulations. And the less regulations the better. Not only does bio-pharming impose all the regulations that are imposed on GMO crops, but there are also additional regulations that are put on top of that because of the drugs that are manufactured within the plants. You have the EPA, federal regulations, and then the state itself can also impose other regulations on top of that."
  - (2) Organic rancher: "There's a history in agriculture that the practitioner on the farm is the last guy to make any money. What makes this any different if the pharmaceutical companies are the ones pulling the strings?"
- Yet some meeting attendees said bio-pharming might have the potential to help agriculturalists and rural Colorado communities.
  - (5) Economic-development specialist: "I'm very interested in seeing how southwestern Colorado may fit into this industry. It may be an opportunity for a new industry here.

Bio-pharming focus group in Walsh, Colo., May 18, 2004

13 participants from southeastern Colorado; 12 men, 1 woman.

- 4 conventional farmers
- 3 county commissioners
- 2 conventional farmer/county commissioners
- 1 economic-development specialist
- 1 extension agent
- 1 employee, agricultural experiment station
- 1 organic farmer

(Participant quotations come from a meeting transcript and are provided to illustrate themes that emerged during the two-hour community discussion. For confidentiality, participants are identified by number instead of name.)

Summary:

- This discussion had a clear premise: Participants were interested in capitalizing on state assets – including the ability to isolate and successfully grow bio-pharm crops – to improve economic well-being for agricultural communities in southeastern Colorado. Most participants indicated that they trust the safety of agricultural biotechnology if it is closely regulated with risk-abatement protocols. Discussion participants said they believe that contamination issues are significant mainly because the public has misconceptions about genetically modified organisms, including bio-pharming; misconceptions, participants said, could lead to significant and negative market impacts for all crops. All participants repeatedly called for independent research that would identify safety risks, determine appropriate cultivation regulations, and counter negative public perceptions that could hinder the benefits of bio-pharming for rural economies and human health. Attendees said widespread economic gains from bio-pharming could be realized only by attracting both cultivation and processing facilities to Colorado. They suggested an incremental approach to build success and public confidence.

Main themes, in order of frequency mentioned:

- Discussion participants agreed that scientifically independent, peer-reviewed research is needed to help determine appropriate cultivation requirements and a regulatory structure that would mitigate potential risks of bio-pharming. Such research also would help perfect the technology by identifying, for instance, biological checks on gene flow. Attendees agreed that research findings must be provided to state residents to educate the public about bio-pharming risks and benefits, and to help build confidence in the technology. Public education about bio-pharming, they said, should highlight potential health benefits for people. An organic farmer at the meeting stressed that research must be independent of industry and interest groups if its outcomes are to be trusted.
    - (3) Conventional farmer: "Information sharing, to the degree that it's feasible, will educate the general public on the issue."
    - (2) Conventional farmer: "That's the secret to the whole thing, the education process. Take Bt corn. In my opinion, if they had taken more time to educate not only the U.S. but the foreign countries about what it actually was, I don't think it would be nearly as negative a response as we've had."
    - (7) Conventional farmer and county commissioner: "That's where our research universities come into play. From a public-policy standpoint, you need to have the proper amount of publicly funded research entities involved in the process and helping disseminate the information. Because if Monsanto is the only one out there putting it

out, it will be suspect worldwide. You should have land-grant institutes across the United States that are in agreement that this is a reasonable way to do something, and that these safeguards are in place on the production end."

(1) Organic farmer: "To get to the heart of this, you have to start asking questions about the problems we create through the gene-insertion process. We hear propaganda: We've been growing and eating these GMOs for ages, 15 years now, and nobody's died. But … there are questions that aren't being answered by the industry and are being ignored in order to push this technology forward. I'm highly skeptical of the association between the USDA, the industry and the universities."

- (10) Extension agent: "That's a concern. I work for a university, and that's a concern of mine. It gets back to the perception, whether true or perceived, there's a perception that if you take money from Monsanto or one of these companies, you might bias your research so you get funding again next year."

- Participants agreed that public concern about genetically engineered crops, including bio-pharm crops, could result in economic risks for Colorado. Attendees said fear of bio-pharm failures and unintentional impacts on the food supply and environment – even if unfounded – could hinder bio-pharming and undermine markets for all Colorado crops. Negative public perceptions could affect markets for conventional crops, seed crops and organic crops, participants said. Export markets were a particular concern.
  - (12) Employee, agricultural experiment station: "They're afraid of having contamination in the food supply. This is what they're afraid of."
  - (13) Economic-development specialist: "Sometimes we get into the fearful mode and can't progress to a mode where we actually have real good productivity."
  - (8) Conventional farmer and county commissioner: "A lot of it would be the vocal minority. A lot of times the silent majority never gets heard, but the vocal minority is what rules. That's what happens when you get a lot of publicity on this. … That 4 or 5 percent that are against it, they are against anything and everything."
  - (7) Conventional farmer and county commissioner: "Monsanto just shelved their Roundup Ready wheat because of their concern over the marketability of the U.S. wheat crop because so much of it goes to foreign markets. That's a perception on the part of our buyer. But if you don't listen to your customer, you're going to go broke. Is that good or bad? I think it points out that public opinion and our purchasers have a lot to say about it."
  - (1) Organic farmer: "Here we get to those perceptions. I'm an organic farmer, and my customers are fanatics. I kind of walk the fences of conservative country boy, and I sell produce to liberal environmentalists. The perception that we may get some contamination creates a real risk for me."
  - (3) Conventional farmer: "I think with bio-pharming, the risks to the organic growers are not greater than the risks to the conventional non-bio-pharming farmer. I think that's important to note. You need protocols with bio-pharming to make sure that either conventional or organic crops are not contaminated."

- In discussing potential economic benefits from bio-pharming, meeting participants noted that few farmers likely would grow the crops and few acres would be cultivated. For these reasons, attendees advocated attracting processing facilities as a route to economic development. They also viewed profit-sharing as a route to broader economic benefit. That said, some participants noted that boosting the finances of a single farmer in rural Colorado could help his or her community. Participants said locating processing near bio-pharm fields could further enhance controls on potential gene flow and commingling; they saw this as a persuasive reason to process bio-pharm crops where they are grown.

- (7) Conventional farmer and county commissioner: "One of the concerns I have is that we'll also be able to have economic advantage of processing the end product in our area. Some concerns I've heard in the past is that they use Colorado for a laboratory and perfect it. Once the product is improved upon, and all the questions are answered, then [the Midwest is] where production will actually go to, as well as the processing."
- (3) Conventional farmer: "Because of the desire to keep these bio-pharming crops fairly isolated and fairly controlled, there probably is a good chance we can have some of the processing pretty close to where it is grown. Less transportation means less opportunity for crops to get out."
- (13) Economic-development specialist: "Maybe that could be a policy – you grow it there, you go into full production there."
- (9) Conventional farmer: "I hope the farmer is justly compensated in what he does."

- Discussion participants advocated incremental introduction of bio-pharming with strict oversight. They agreed this approach would prove the technology's safety and counter public fear.
  - (2) Conventional farmer: "I would sure feel a lot more comfortable with [employee, agricultural experiment station] growing some of it for a period of time and seeing how he gets along. ... If it's positive, then we try it on our fields. That's what needs to be done with this. We're fortunate that our research center is pretty well isolated."
  - (6) Conventional farmer: "I agree. That was one of the concerns, where you have pushed it out too quick. That generates fuel for the fire for policy issues."
  - (10) Extension agent: "I think we've tried to push things too hard, too fast."
  - (1) Organic farmer: "The problems could probably be worked through if we were willing to take the time. But we seem to be pushing this technology a little too fast, in my opinion."
- Most discussion participants viewed bio-pharming, if developed under appropriate risk-mitigation protocols, as holding economic potential for their southeastern Colorado agricultural communities.
  - (2) Conventional farmer: "With the farm economy being depressed, farmers need something that will generate a profit. Our communities are drying up, and we need to take a look at all possibilities."
  - (12) Employee, agricultural experiment station: "Anything that brings in money to our community, especially for crops we already grow, has to be benefit."
  - (8) Conventional farmer and county commissioner: "Especially if there is added value to that crop."
  - (5) County commissioner: "I think anything that we can do to add value to what we raise has got to be beneficial to the people in the county and the county itself. … Rural America is dying: Our county has got 25 percent of our 4,500 people in it who are over 65 years old."
- Participants generally wanted to know more about bio-pharming and indicated that they need reliable information to analyze the technology's potential risks and benefits. They wanted to move beyond perceptions to discussion of established risks and benefits. And they wanted details about bio-pharm cultivation and necessary investments, among other specifics.
  - (11) County commissioner: "I'd like to see what the public policy is, what bio-pharming is all about and what the community concerns are."

- (8) Conventional farmer and county commissioner: "I want to learn more about bio-pharming and what it is exactly and how this is going to help out in the future."

- Also during the meeting:
  - Participants discussed whether federal or state regulations would best allow Colorado farmers and communities to gain greatest benefits with fewest risks from bio-pharming. One argument held that federal regulations would provide the most uniform and effective safeguards; another argument held that state regulations, driven by local stakeholders, would be better tailored to local growing conditions.
  - All participants voiced concern about liability issues and who would bear potential costs.

Bio-pharming focus group in Sterling, Colo., May 27, 2004

13 participants from northeastern Colorado, primarily Logan and Phillips counties; 12 men, 1 woman.

- 4 conventional farmers
- 3 extension agents
- 2 county commissioners
- 1 conventional farmer and county commissioner
- 1 conventional farmer and economic-development board member
- 1 organic farmer
- 1 officer, farming group

(Participant quotations are from a meeting transcript and are provided to illustrate themes that emerged during the two-hour community discussion. For confidentiality, participants are identified by number instead of name.)

Summary:

- Meeting participants, who live and work in counties where Colorado's first two bio-pharming crops were proposed, focused much of their discussion on economic issues. Attendees saw in bio-pharming the potential for rural economic development. They pondered how individual farmers and their communities might position to capitalize on the state's assets for bio-pharming, including growing conditions and the ability to isolate crops, to capture greatest economic benefits with fewest risks. During this strategy-oriented discussion, participants had a number of questions – both general and highly technical – about possible risks and benefits. They wanted reliable answers, including answers about potential liabilities, to ascertain risk-benefit ratios. Participants viewed public fears about bio-pharming as an obstacle to the technology; they viewed those fears, well-founded or not, as a threat to Colorado's existing crop markets. They highlighted need for public education based on facts gained from independent research.

Main themes, in order of frequency mentioned:

- Participants talked in detail about economic development. Most saw the potential for agricultural communities to capitalize on Colorado's assets for bio-pharming, including growing conditions and ability to isolate crops. Participants agreed that bio-pharming would require relatively few acres. They also agreed that attracting bio-pharm cultivation in conjunction with processing, perhaps through a cooperative venture involving grower investment and profit-sharing, would likely yield more widespread economic benefit. Processing plant-made pharmaceuticals where they are grown might provide further controls over gene flow and commingling, a persuasive reason for drug companies to locate in northeastern Colorado, some participants said. Some attendees urged an incremental approach to bio-pharming to better understand its economic benefits and prove its safety; some advocated laying groundwork now to realize future economic gains. Meeting attendees also questioned the costs required to position for future economic benefits. They questioned whether potential economic benefits would justify possible costs, and wanted to analyze those issues.
    - (10) Conventional farmer and economic-development board member: "I'd like to think it would help in multiple ways. Any additional revenue streams that can come into a small community get multiplied. You start out, if a farmer grows it, makes a few extra dollars, that gets passed to the community, and it all changes hands. Anything that brings in additional streams is a great benefit for small communities."

- (12) Extension agent: "Not only is it going to help some of the producers, but it's also going to bring in people in labor that are going to have to have places to stay, that are going to bring in outside money to the community. It's going to be a pretty labor-intensive process throughout the entire growing, and it's going to be highly technical labor."
- (1) Conventional farmer: "There aren't going to be a lot of farmers involved in this. You're going to have a better chance to get in on this as an owner rather than as a producer."
- (2) Conventional farmer: "I think (processing) is where the jobs and the economic development is going to come from. It's going to be important to keep that development where the crops are grown. Because if they load up the 10 or 20 or 30 semi-loads of corn that they grow with the lipase in it and ship it to St. Louis, it's not going to do Phillips County, Colorado, a bit of good."
- (11) Extension agent: "I'd like to echo that sentiment. We take the risk that crops are contaminated, or something bad happens in the production process, but the profits are elsewhere. There's no commitment that the entire business will be here, only that the production is here; the rest of it is always left blank. That's one big fear that's been expressed, that we take all the risk, we get all the negatives, but the profits go elsewhere."
- (3) County commissioner: "That's one of my concerns with this project. If it would work, then the people that live out here and do the work, and they don't profit somewhat by this new adventure, see somebody else come in and make all the profit and we do the work, and walk out. That won't feel very good. … That's why it would be nice to be part of the whole thing, a cooperative venture, if you were going to do it."
- (4) Officer, farming group: "The communities need to sell them on the idea of rent, housing, the school systems we've got; you'd be better off in this area. Ship out the manufactured product rather than shipping out the raw product."
- (7) County commissioner: "From what I hear, a major part of the economic portion of this would be from the processing, manufacturing or whatever. What I haven't heard is how this process is done. What kind of process do we go through to do the manufacturing, processing? I would like to see exactly what kind of costs we would be looking at as a community in doing this."

- Participants discussed many details related to risks. Most were generally confident about the ability of research-driven safeguards to prevent inadvertent bio-pharm gene flow and commingling. Some participants wanted to know more about the technology and potential safety risks; they wanted to understand opposition. Participants raised a variety of technical questions in their risk discussion: They talked about pollen drift, insect pollinators, weedy relatives, temporal isolation to control gene flow, growing time needed for viable protein, dedicated equipment, the number acres needed for bio-pharming now and in the future, potential problems with wildlife like rodents and deer, irrigation demands, geographic isolation requirements, and the handling of biomass and byproducts.
  - (14) Conventional farmer: "What is the negative vs. the positive? I don't know. I'm eager about it, as a question."
  - (2) Conventional farmer: "I think there's some technological concerns and biology concerns about gene flow and gene transfer outside of the control of the particular crop area. I have enough faith in protocols, and enough faith in the regulatory process, to see that it doesn't happen."
  - (1) Conventional farmer: "The public seems to be most concerned about the pollen. I don't see the pollen as being a big problem because you've got several mitigators there. But residual grain left in the field, I still have a little concern about rodents or birds or something carrying that off. I don't know how to solve that problem."

- (8) Conventional farmer and county commissioner: "I see the public wondering, what are we going to do with the byproduct? How are we going to assure them that there's nothing left in the byproduct when we try to figure out, would it be composted? Would you feed it? You're going to have a lot more of the residue than the product."

- Attendees identified public fear of genetic engineering and bio-pharming, well-founded or not, as an obstacle to developing the technology and realizing potential economic benefit. Participants were uniformly concerned about the potential for negative public perceptions to harm existing Colorado crop markets.
  - (1) Conventional farmer: "Public perception is a huge obstacle we have to overcome."
  - (10) Conventional farmer and economic-development director: "Anymore, perception is reality. When you have bio-anything, people are automatically apprehensive. … I think one of the scariest things is if we go ahead and try to do this and it fails, you'll never get anybody willing to try it again, or try anything new again."
  - (12) Extension agent: "People believe the 30-second sound bite on CNN, where all they talk about is 'Frankenfoods.' … I think one of the biggest problems right now is, just like (#10) said, is that perception is reality, whether it's dangerous or not."
  - (2) Conventional farmer: "The biggest disaster that's happened in the last five years is StarLink. That was a huge outcry. You could have eaten 10 tons of StarLink tacos and it wouldn't have hurt anybody, but it wasn't fully approved for consumption. … The whole market-acceptance problem has killed Roundup Ready wheat. That comes back to educating not only consumers – consumers worldwide – but importers and everybody else."
  - (11) Extension agent: "The risk is loss of marketability of the product you produce because it's contaminated in one way or another, or perceived to be contaminated. It's not that you get a lower price, it's that you can't sell it."
  - (1) Conventional farmer: "The extension of that is that if the importers of our product think there's a hazard of that happening, even when it doesn't, and the value of our market goes down."

- Discussion participants roundly called for reliable information to answer their own questions, to counter public fears and to determine appropriate bio-pharm regulations. They identified a need for public education based on facts from independent research. Some participants said public education should highlight bio-pharming's potential benefits for human health.
  - (3) County commissioner: "It seems to me like there's a lot of concern on how this product is going to be produced, but do we have any experts? Someone who could really tell us how this could work? ... We really need some information that's accurate. … (Are the fears) justified or not? That's my concern."
  - (7) County commissioner: "I think that we've all probably had concerns with the safety factor, but I think as we get more research done and more studies done on this, a lot of those things are going to be resolved. Most everything that comes out new has got a fear factor attached to it, but as we research it, we find that most of those didn't come to fruition, that they were something that we didn't really need to be concerned about."
  - (10) Conventional farmer and economic-development board member: "The regulations will come with the science involved. … Different technologies are going to require different regulations, different processes."
  - (14) Conventional farmer: "If you have this company and they come up with a set of things that they're planning to do – if the information is all company-generated, we develop skepticism. Why can't CSU and CU take their facts apart and come up with some degree of validity?"

- Participants raised questions about legalities, including liability issues and intellectual property rights to patented genes. They also voiced concern about the potential for bio-pharm sabotage and questioned who would bear any costs.
    - (9) Extension agent: "If you were a farmer and you were going to take a contract, would you want an 'Act of God' clause? Because we all know what hail does. If you segregated a field and you said, I'm going to put it on this many acres, and you're manipulating that buffer, you want to be paid for at least the attempt, whether you raise the crop or not, don't you?"
    - (6) Organic farmer: "You really have a problem there if you get hailed out, because all that's on the ground. Then there's more than just the loss of a crop."
    - (4) Officer, farming group: "One of my concerns is making sure the farmer himself is not liable for some of this stuff because, regardless of what he gets paid for what he's going to manufacture, the liability could be 40 times more than the profit he ever got out of it. … That's been my big concern – to make sure the farmer doesn't have to stand liability behind him."
    - Conventional farmer: "What about security? Some people here are county commissioners. We're going to have to get involved in security because there are risks there."
    - (11) Extension agent: "They have saboteurs that make it a point to go out and wipe out these crops."
    - (10) Conventional farmer and economic-development board member: "Confidentiality is an issue. … If that location is disclosed, then you open yourself up to people coming in and destroying the field, that kind of thing."
    - (12) Extension agent: "What are going to be the penalties for somebody if they get caught tampering with or destroying a field? I think that's something that needs to be addressed. … I think it needs to be a pretty stiff result."
- Also during the meeting:
    - Participants said use of non-food crops for bio-pharming might reduce some risks but could pose other problems, including cultivation difficulties.

APPENDIX B

Summary of some crops that might be used in Colorado

A move to integrated bio-pharm activities – including research and development, crop cultivation and processing – would likely begin with successful cultivation of bio-pharm crops in Colorado. Here's a look at some of the crops that might be considered, and the settings in which they might be grown:

Corn: Bio-pharm experimentation most often uses corn grown in open fields, with proteins of interest expressed in corn seeds. That's chiefly because scientists understand the corn genome better than that of most other crop species, and likewise know how to successfully insert genes into corn. The crop grows very well under irrigation in Colorado. And, as the state's first two permit applications suggest, bio-pharm corn grown on the state's Eastern Plains can be isolated from commodity corn grown for human food and livestock feed. But corn presents some disadvantages as a bio-pharm crop: It is a major crop on the Eastern Plains and the Western Slope, and a plant commonly grown in home gardens (Colorado Agricultural Statistics Service, 2003). That means, depending on the proposed location of a bio-pharm corn plot, sexually compatible corn could be in the area, presenting the possibility of cross-pollination and the unintended spread of novel genes. However, corn has no cross-compatible wild relatives in Colorado. Corn plants produce abundant pollen that potentially can travel long distances, although at very low levels. An Oklahoma study found 32 percent cross-pollination at 1,640 feet (Jones and Brooks, 1950), well beyond the USDA's 660 foot isolation guideline for keeping cross-pollination below 0.1 percent (National Research Council, 2000). After reviewing the available data from an aerobiological framework, Aylor et al. (2003), conclude that corn pollen dispersal is described by a long-extending "tail," subject to high variability, but potentially resulting in cross-pollination at significant distances from the source. There are at least four ways pollen production typically is controlled in bio-pharm corn: manual detasseling, or removal of the plant's pollen-producing organ before pollen is mature; male sterility, in which plants produce only sterile pollen; isolation of bio-pharm corn from commodity corn by at least one-half or 1 mile; and later planting, called "temporal isolation," meaning that when pollen sheds from bio-pharm corn, it is too late in the growing cycle to cross-pollinate other corn in area. The growing season for corn is relatively short in Colorado, especially in the northern half of the state. To mature and dry down properly, the bio-pharm protein will need to be produced in relatively early maturing hybrids, rather than in Corn Belt maturity corn. Open fields are the most logical setting for bio-pharm corn because greenhouse-grown corn has low yields and pest problems.

Potatoes: Potatoes offer advantages similar to those of corn. The crop grows well in irrigated fields in the San Luis Valley and on the Eastern Plains, making Colorado the country's fourth-largest potato producer (Colorado Agricultural Statistics Service, 2003). Scientists have developed some bio-pharm applications in which pharmaceuticals are expressed in potato tubers (Canadian Food Inspection Service, 2001). The potential spread of novel genes through drifting pollen is less a problem with self-pollinated potatoes than with cross-pollinated corn because potato pollen is less abundant and shed is mostly within closed floral structures. Potato has no cross-compatible wild relatives in Colorado. But the potato industry has been cautious about genetically engineered potatoes of any kind, let alone bio-pharm potatoes. Why? In contrast to corn, most of which is grown for livestock feed, virtually all potatoes are grown for direct human consumption. In the bio-pharming context, that could at least slightly raise the risk for pharmaceutical potatoes to enter the human food supply.

Tomatoes: Tomatoes grow successfully in Colorado greenhouses in the winter. That presents the possibility of an enclosed setting for cultivation of bio-pharm tomatoes, which have been developed to express therapeutic proteins in their fruit. In an example of this approach, Arizona State University is using greenhouses to grow bio-pharm tomatoes that produce vaccines (Derra, 2004). Bio-pharm tomatoes probably could not be grown in open fields in Colorado because the state has a relatively short growing season and comparatively low nighttime temperatures, which delay tomato maturity. Like potatoes, tomatoes are a crop grown for direct human consumption; that raises some questions about possible risks for the human food supply. Also like potatoes, they are primarily self-pollinated and do not cross-pollinate any wild species in Colorado. At Arizona State University, scientists have worked to address that issue by developing white tomatoes for bio-pharm applications, providing a visual marker to distinguish the unique fruit. The enclosed growing environment of a properly designed and equipped greenhouse might help address potential contamination risks by providing more controls over novel genes than are possible in an open field.

Tobacco: Tobacco is an attractive vehicle for bio-pharming because, as a non-food crop, it might be less likely to enter the human food supply (although people do ingest tobacco through cigarettes and other products). Scientists also are adept at engineering genes in tobacco. Research with bio-pharm tobacco is well-advanced because of interest in developing alternative uses for the crop in Southeastern states. Tobacco also can be used two ways to produce plant-made pharmaceuticals: It can be genetically engineered to produce medicinal proteins, and its leaves can be rubbed with deactivated viruses to trigger production of pharmaceutical proteins in leaves. The latter approach prevents production of pollen and seeds containing novel genes, which could help reduce potential contamination risks. Tobacco would not grow well in open fields in Colorado because of the state's dry climate and short growing season. Greenhouse cultivation might be an option for bio-pharm tobacco in Colorado, although pests are typically a significant problem with greenhouse-grown tobacco.

Alfalfa: Alfalfa produces a large amount of plant material, so it could be an efficient crop for leaf-produced pharmaceuticals. Alfalfa is widely adapted in Colorado and is one of the state's most valuable feed crops, especially for dairy cattle and horses (Colorado Agricultural Statistics Service, 2003). This might raise questions about potential safety risks. However, the most obvious potential concern with alfalfa is that it's a persistent perennial, meaning, in contrast to an annual plant, it may be more difficult to eliminate the plant completely from a production field after the final harvest. Alfalfa is largely insect-pollinated, so pollen from bio-pharm crops could be widely disseminated and potentially could cross-pollinate other alfalfa plants, again presenting the potential for inadvertent spread of novel genes; bees, for instance, can carry pollen at least two-thirds of a mile (McGraw, 2001). Beekeepers have raised concerns about the possible effects of bio-pharm alfalfa on bee health.

Algae and duckweed: Scientists recently have started investigating production of pharmaceutical proteins in algae and duckweed. These aquatic plants can be grown in tanks. This system offers the advantages of a non-food host species and the controls of an enclosed setting. Bio-pharm algae and duckweed could be grown in greenhouses, mine shafts or warehouses with appropriate temperature and light conditions. Research with these plants is in its infancy, and economic and technical feasibility must be demonstrated (Mayfield et al., 2003).

APPENDIX C

Potential legal claims

Products Liability: Causes of Action and Claims

Tort

1. Failure to warn

2. Trespass and nuisance (land or body)

Nuisance occurs when someone interferes with another person's use and enjoyment of his or her property. The interference is generally an act that results in unwanted or undesirable substances resulting in a diminution of expected use emanating from the defendant's property and sensed from the other person's land. The interfering act does not need to cause property damage, but must affect the ability to use and enjoy his or her property. GMO contamination could effect which crops a neighboring farmer may grow, thereby interfering with the farmer's ability to use his property.

3. Strict liability under Restatement of Torts 402 A

Strict liability arises when a person or entity engages in an abnormally dangerous activity; one harmed by the abnormally dangerous activity can recover damages from the actor, without having to prove that the actor was reckless or negligent. For example, if a farmer and/or seed company knows that a GMO crop is difficult to control and that it will likely cross-pollinate with crops in adjacent fields, the farmer and/or seed company may be held strictly liable for any resulting damages. The injured party will not be required to prove duty or breach of duty.

Courts assessing genetic contamination claims based on strict liability may compare them to past pesticide drift cases. In a 1977 Washington State Supreme Court case, the court held that an aerial spray company that allowed pesticides to drift onto an organic farm was strictly liable for damages to the organic farm.

4. Ultrahazardous activity

5. Defective design (whether the product is unreasonably dangerous as tested by a consumer's expectations). The duty of non-negligence: "A manufacturer who fails to exercise reasonable care in the manufacture of a chattel, which … he should recognize as involving an unreasonable risk of causing physical harm to those who use it for purposes which the manufacturer should expect it to be used and to those to whom he should expect to be endangered by its probable use, is subject to liability for physical harm caused to them…."

6. Negligent Design: A determination of whether a manufacturer has negligently designed its products requires a finding of fact by balancing the probability of harm, the magnitude of the probable harm, the risk of harm, and the effects that the adoption of an alternative design would have on the monetary cost, efficiency, utility, and other attributes of the product. This has become the essence of the "risk-utility" analysis of the Restatement (Third) of Torts.

California Jury Instruction 14:19 (1997):

"A product is defective in its design, even if it is manufactured and performs exactly as intended, if any aspect of the design makes the product unreasonably dangerous."

7. Defective manufacturing

8. Negligence per se

Negligence arises when a person fails to act reasonably under the circumstances and this failure causes harm to another. The elements of a negligence claim are: (1) the existence of a duty on the part of the defendant to protect plaintiff from injury; (2) failure of defendant to perform that duty; (3) injury to the plaintiff resulting from such failure; and (4) damages. To prove that GMO contamination was the result of negligence, one would have to prove that a neighboring landowner, or the bio-pharm seed company, had a duty to prevent GMO contamination and that there was a reasonably foreseeable likelihood of injury. Given the potential for certain GMO crops to contaminate neighboring fields, a court could find that the bio-pharm seed company and/or farmer have a duty to prevent contamination injury. Failure to properly select or design seed, adhere to specified buffer zones, or follow growing and harvesting procedures indicate a breach of that duty.

9. Negligent infliction of emotional distress

10. Negligent misrepresentation

11. Wrongful death

12. Unfair or deceptive trade practices

13. Negligent testing (failure to test product; failure to test and then warn genomic subpopulations)

14. Tort-based toxicogenomic law suit based on genomics, epigenetics that identify cause and effect, exposure and result. This toxicogenomic concept links exposure, biomarkers and gene expression, and the probability of disease as a means to recover damages.

Causation/Evidence Standards

Federal Courts

Federal Rules of Evidence 702 provides in all federal court cases that the court is a gatekeeper to admit only reliable evidence as to causation; that is, the evidence must be reliable, peer reviewed, replicable, whether the method has a known potential rate of error, and more than merely generally accepted in the relevant community of scientists.

"If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, provided that (1) the testimony is sufficiently based upon reliable facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case."

State Courts

State standards mostly have adopted and maintained the Frye v. United States, 293 F. 1013 (D.C. Cir. 1923) test for admissibility of scientific evidence; that is, an expert's testimony may be admitted to prove causation if the theory or method which is the subject of the testimony has gained general acceptance in the relevant scientific community. This admissibility standard of evidence coupled with the "general causation" standard in many other states, including California, permits a toxic tort plaintiff to get to the jury on a doctor's testimony that the injury or disease was caused more likely than not by exposure to the chemical or substance.

Cases

Bockrath v. Aldrich Chemical Co., 980 P.2d 298, Supreme Court of California, July 29, 1999. Plaintiff sued 55 defendant chemical manufacturers from workplace exposure. Sets pleading standards for chemical exposure and injury; the plaintiff must prove that the defective products were a substantial factor as test for causation of injury. "…(A) very minor force that does harm is a substantial factor."

Cassidy v. Smithkline Beecham Corporation, Pa. Ct. of Common Pleas, Chester County, No. 99-10423, filed December 14, 1999. Settled July 1, 2003. Class action filed on behalf of a subpopulation of individuals with gene type HLA-DR4+ who had been given the LYMErix Lyme disease vaccine and who may have been at risk of developing arthritis. LYMErix withdrawn from market, SKB to pay $975,000 fees and $147,000 costs to plaintiffs' lawyers, and plaintiffs did not relinquish potential personal injury and economic damage claims. No class plaintiff demonstrated any injury from the vaccine.

John Castillo, et al., v. E.I. Du Pont, et al., No. SC00-490. Supreme Court of Florida. Opinion filed July 10, 2003. Rehearing Denied September 4, 2003. Held: that the expert testimony offered by the Castillos at trial was admissible under Frye v. United States, 293 F. 1013 (D.C. Cir. 1923). This case involves a products liability and negligence claim against E.I. Du Pont de Nemours & Co., Inc. (DuPont), the manufacturer of Benlate, and Pine Island Farms, Inc. (Pine Island), the owners of a "you-pick" farm that used Benlate and operated in the petitioners' neighborhood. Donna and John Castillo alleged that when Mrs. Castillo was seven weeks pregnant, she was exposed to Benlate, an agricultural fungicide used by Pine Island. They further alleged that benomyl, the active ingredient in Benlate, entered her bloodstream and caused microphthalmia, a rare birth defect involving severely underdeveloped eyes in her unborn son.

Daubert v. Merrill Dow Pharmaceuticals, Inc., 951 F. 2d 1128 (9th Cir. 1991). Plaintiffs Jason Daubert and Eric Schuller suffer from limb reduction birth defects. They allege that these defects resulted from the fact that their mothers used Bendectin, a prescription anti-nausea drug, during pregnancy.

Daubert v. Merrill Dow Pharmaceuticals, Inc., 43 F. 3d 1311 (9th Cir. 1995). On remand from the United States Supreme Court, the Court stated instructions regarding admissible testimony: "ensuring that an expert's testimony both rests on a reliable foundation and is relevant to the task at hand." *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 113 S.Ct. 2786, 2799, 125 L.Ed.2d 469 (1993).

Delhite v. United States, 346 U.S. 15, 53 (1953). Action against the United States to recover damages for death resulting from the explosion of ammonium nitrate fertilizer produced under the control of the United States. U.S. District Court's analysis of the specific aspects of the manufacture was foreshadowed by a theory of foreseeability of the risk: "This record discloses blunders, mistakes, and acts of negligence, both of omission and commission, on the part of Defendant, its agents, servants, and employees, in deciding to begin the manufacture of this inherently dangerous fertilizer."

Greenman v. Yuba Power Products, Inc., 377 P.2d 897, Supreme Court of California, 1963. A manufacturer placing a product in the stream of commerce has a legal duty to prevent defects causing injury.

Jenkins v. Platte Chemical Company, et al., Supreme Court of Kansas (1994) 886 P.2d 869. Complaint in products liability, design defect that 2, 4-D caused farmer/plaintiff's multiple myloma cancer. Court held that FIFRA pre-empted some claims and that consumer could not prevail on strict liability design defect claim without identifying what aspect of the manufacturers' product was defectively designed.

Leach v. DuPont, Wood County Circuit Court, West Virginia, Civil Action No. 01-C-608. Proceedings pending in class action products liability suit for water contamination with perfluorooctanoic acid (PFOA/C-8) 1) potential liability for thousands of claimants, 2) medical monitoring, 3) ground and surface water contamination from chemical production facility, 4) allegation of document destruction and failure to keep adequate records.

People v. Kelly 17 Cal. 3d 21 (1976) and People v. Leahy 8 Cal. 4th 587 (1994) expressly rejecting Daubert in favor of Frye standard of expert testimony admissibility.

Sleath v. West Mont Home, 16 P.2d 1042, Supreme Court of Montana, December 28, 2000. Failure to warn claims in negligence, strict liability, and breach of express warranty not preempted by FIFRA. "Congress did not intend to extinguish common law remedies or actions for damages." Complaint for personal injury as a result of alleged exposure to Dursban. The claim and lawsuit was permitted to go forward.

Turner v. Chevron Corporation, et al., Superior Court, State of California, County of Los Angeles, Case No. BC256293. Filed August 16, 2001. Complaint by CalTrans worker for personal injury as a result of exposure to pesticides over a 20-year period. Complaint identifies 92 products, 56 active ingredients, produced by 42 different manufacturers, sold by 15 different distributors. Complaint in strict liability – design defect, negligence, breach of implied warranties, battery, loss of consortium.

Articles and treatises

Uniform Commercial Code. § 2-318, "Third Party Beneficiaries of Warranties Express or Implied." "Alternative C": A seller's warranty whether express or implied extends to any person who may be reasonably expected to use, consume, or be affected by the goods and who is injured by the breach of the warranty. A seller may not exclude or limit the operation of this section with respect to injury to the person of an individual to whom the warranty extends.

Restatement of the Law Second. American Law Institute, 1964. Torts, Products Liability 2(b): "… (A) product is defective in design when the foreseeable risks of harm posed by the product could have been reduced or avoided by the adoption of a reasonable alternative design by the seller or other distributor, or a predecessor in the commercial chain of distribution, and the omission of the alternative design renders the product not reasonably safe. …"

Restatement of the Law Second. Torts: § 402A. The American Law Institute. "Special Liability of Seller of Product for Physical Harm to User or Consumer." This marked for the first time the Institute's recognition of the privity-free strict liability for sellers of defective products. Emphasis was to eliminate privity so that a user or consumer, without first having to establish negligence, could bring an action against a manufacturer, as well as against any other member of a distribution chain that had sold a product with inadequate warnings.

Restatement of the Law Second. Torts: § 402A, comment j. The American Law Institute. "Where a warning is given, the seller may reasonably assume that it will be read and heeded; and a product bearing such warning which is safe for use if it is followed, is not in defective condition, nor is it unreasonably dangerous." Restatement of the Law Third. Torts: § 2, comment 1 expressly rejects the Restatement Second warnings approach: "When an alternative design to avoid risks cannot be unreasonably implemented, adequate instructions will normally be sufficient to render the product reasonably safe."

Reference Manual on Scientific Evidence, Federal Judicial Center, (1994); Second Ed. 2000. West Group.

Toxicology, epidemiology, survey research, statistics, multiple regression, economic losses and damages. Discussion of Daubert v. Merrel Dow Pharmaceuticals, Inc., standards of admissibility and reliability of scientific evidence and expert opinions. Daubert and progeny specified in Federal Rules of Evidence, 702, Testimony by Experts.

"Causality in Epidemiology, Health Policy, and Law," Environmental Law Reporter, 27 ELR 10279, June 1997.

Gary E. Marchant, "Genetic Susceptibility and Biomarkers in Toxic Tort Litigation" 41 Jurimetrics 67 (2000).

"Epidemiologic Proof in Toxic Tort Litigation," Black and Lilienfield, 52 Fordham Law Review 732, 1984.

General and Applied Toxicology. Ed. by Ballantyne, Marrs, Turner. Stockton Publishing. 1995.

The Merck Manual of Diagnosis and Therapy. Seventeenth (Clinical) Edition. 1999.

Toxic Tort Litigation, Greer and Freedman, Prentice Hall, 1989.

Gary E. Marchant, "Genomics and Environmental Regulation. Scenarios and Implications." Center for the Study of Law, Science and Technology, Arizona State University College of Law. January 2000.

Glossary

Epidemiology

Epidemiology is evidence of an association of events that occur more frequently than would be expected by chance. Thus, epidemiological evidence of an association between exposure and disease, that are not merely temporal, is some statistical evidence of a causal relationship. However, although epidemiology describes an association between a chemical or substance and a population, it alone does not alone prove causation.

Epigenetics

The study of heritable changes in gene function that occur without a change in the DNA sequence. The study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence. Epigenetics attempts to describe the inheritance of information on the basis of gene expression, in contrast to genetics, which attempts to describe the inheritance of information on the basis of DNA sequence.

Genetic variability (SNP)

Single nucleotide polymorphisms constitute the majority of genetic differences among individuals and influence disease susceptibility and therapeutic response.

Polymorphism

Thompson & Thompson, Genetics in Medicine, 6th ed. (at 87). Polymorphisms are not necessarily uncommon: "…(D)ifferent versions of a particular DNA sequence at one particular chromosomal location (**locus**) are called **alleles**. When alleles are so common that they are found in more than 1 percent of chromosomes in the general population, the alleles constitute what is known as genetic polymorphism. In contrast, alleles with frequencies of less than one percent are, by convention, called **rare variants**."

Statutes of limitations and latent disease

Limitation on time for filing a cause of action. Two years in most states, except California, which has a one year for SOL in negligence. Ohio, for example, has a four year SOL for asbestosis. Most states have adopted a discovery test for latent disease: Once the plaintiff reasonably knows or should know that there is a suspected association between exposure to a substance and his disease, he has from that point until the term of the statute of limitations to file a complaint. Thus, if a doctor suggests to the plaintiff a link, then that time starts the statute of limitations.