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

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Summary 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 could 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 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 might be successfully 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 the science of 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).

The technology uses crops such as corn, soybeans, rice and tobacco to produce specialized proteins for pharmaceuticals. Production of these proteins is possible because bio-pharm crops are engineered to contain genes from mammals, microorganisms or other plants, resulting in modifications that do not naturally occur in plants. Bio-pharming presents potential risks because the 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 existing markets for other crops ("Drugs in crops," 2004; Flinn and Zavon, 2004).

Indeed, safety 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 interested in and potentially affected by bio-pharming. Many participants identified economic development as bio-pharming's chief potential benefit for Colorado; they agreed the state would need to minimize potential risks for human health, the environment and existing crop markets for the technology to move ahead.

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 greatest benefits with fewest risks.

Why Colorado?

Bio-pharming emerged in Colorado in spring 2003, when the U.S. Department of Agriculture (USDA) granted a permit to Meristem Therapeutics of Clermont-Ferrand, France, to grow 30 acres of bio-pharm corn on the state's northeastern plains. The Colorado Department of Agriculture concurred with the USDA's decision. The corn would have produced a therapeutic protein, an enzyme called lipase, to treat digestive problems in patients with cystic fibrosis (Mison, 2004). But the permit was granted too late for the 2003 growing season, and the plan did not move ahead (Auge, 2003a, 2003b).

In spring 2004, Colorado's first bio-pharm crop – comprising about 2,000 genetically engineered corn plants – was sown on a 90-foot-by-35-foot plot in Logan County, also on the northeastern plains. An Iowa State University researcher received a federal permit to grow the bio-pharm crop as part of research to develop a corn-based edible vaccine system for livestock. The Colorado Department of Agriculture (2004) again concurred.

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. Colorado has several conditions that make it attractive for bio-pharming:

- The state presents **relative ease in assuring isolation** for open-air bio-pharm crops, such as corn. 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.
- 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.
- Colorado 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.
- Colorado's **agricultural heritage** presents a tradition of farming know-how and success, placing agriculture among the top industries in the state.
- Colorado has a **thriving scientific community**, an infrastructure of training and research facilities, and a vibrant biotech business community.

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 the 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). Another method for obtaining

biopharmaceuticals is to extract them from animal and human tissues. But these are high-cost procedures that carry the risk of transmitting infectious diseases to human recipients. And current methods for mass production of medicinal proteins are not sufficient to meet all potential needs (Huang, 2000; Walsh, 2000).

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). The biotech industry believes it could quickly and effectively respond to rising demand for treatments by planting more bio-pharm acreage (Pew Initiative on Food and Biotechnology, 2002).

The market potential of bio-pharming and the state's first two bio-pharming proposals suggest 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).

What are the benefits of bio-pharming?

Economic development is the main benefit that might be realized from bio-pharming in Colorado. The state likely will achieve 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).

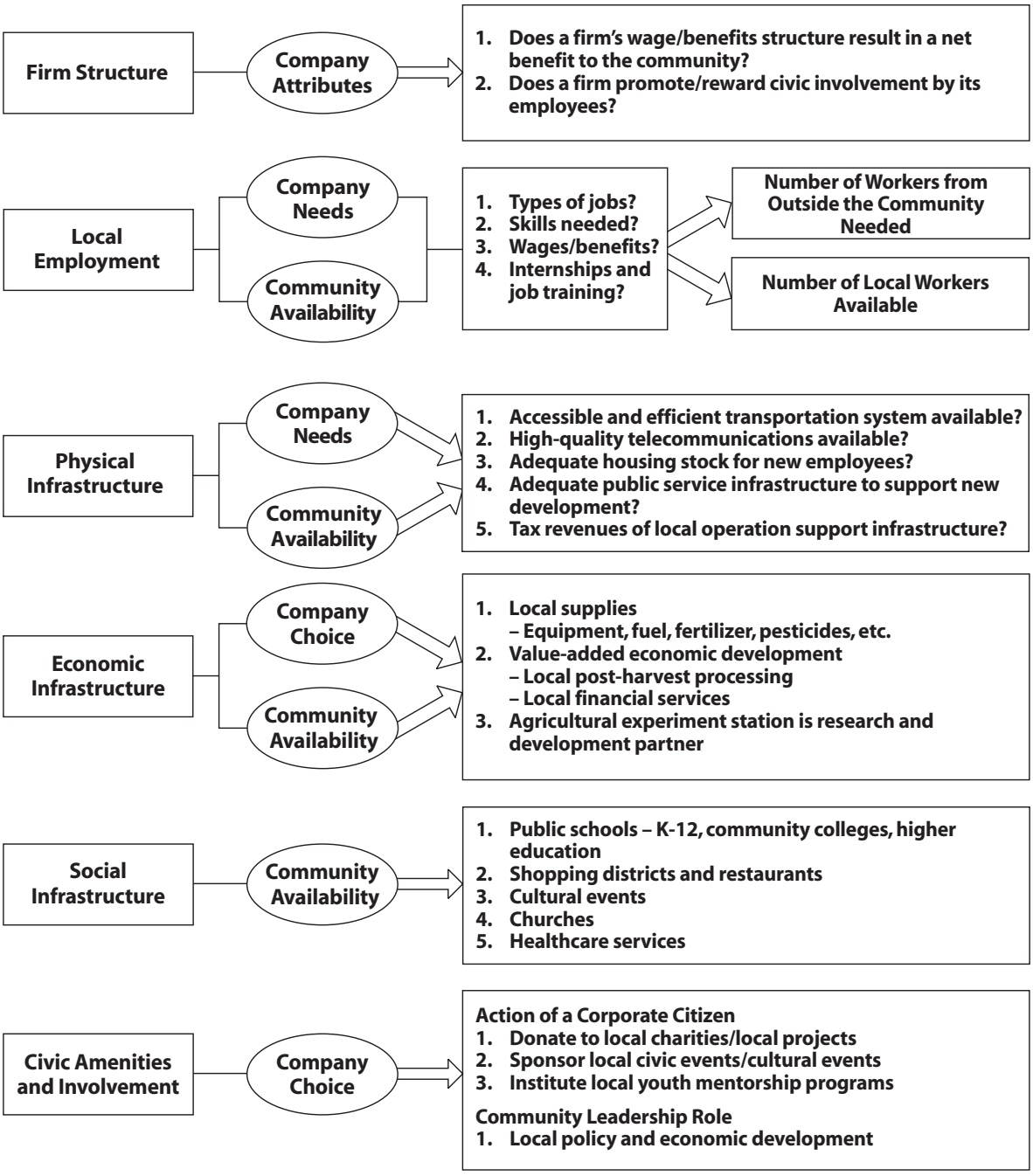
During Colorado Institute of Public Policy focus groups in spring 2004, conventional farmers, in particular, expressed hope that bio-pharming could be a springboard to better economic health for individual growers and their communities. Focus group participants in all quadrants of the state were unified in the opinion that attracting bio-pharm processing and related activities to rural Colorado would be the best way to achieve widespread economic gains from the technology; they cautioned that bio-pharm cultivation alone has limited economic benefit.

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 new technology expands. Bio-pharming will require small acreages to produce large quantities of medicinal proteins, and crops will be grown under stringent regulatory conditions. These factors will limit the number of farmers involved.

Economic analyses suggest that drug companies and consumers will gain most from plant-made pharmaceuticals (Duffy 2001; Kostandini, Mills and Norton, 2004). This is why some bio-pharming proponents want Colorado communities to get involved in processing; it could be a route for the state to participate in the bio-pharming production chain and potentially to realize more economic benefit. Economic benefits also could accrue if partnerships develop between pharmaceutical companies and Colorado research facilities. Likewise, less expensive prescription drugs could produce economic benefits for the state and its residents.

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 1) 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 1: What is the potential for economic development?



What are the risks of bio-pharming?

The potential for economic development from bio-pharming represents the benefit side of the decision-making equation. The potential for unintended harm to human health, the environment and existing agricultural markets represents the risk side of the equation.

Risks may arise because plant-made pharmaceuticals are not controlled like proteins cultured in enclosed fermentation facilities (Peterson and Arntzen, 2004). Bio-pharm genes could potentially spread to wild or domesticated relatives through pollen or seed, a process called "gene flow." Likewise,

plant material containing pharmaceutical proteins might accidentally enter human food or livestock feed supplies through commingling during harvest, transport or storage. Such possibilities might pose human-health, environmental and market-related risks. For those reasons, gene flow and commingling are the focus of a growing body of research, bio-pharming regulations and much of the debate over this technology.

Gene flow – the exchange of genetic material through pollen and seed – is a natural occurrence that is not unique to genetically engineered plants. It occurs any time one organism breeds with a related species, thus passing on their combined DNA to offspring (Pew Initiative on Food and Biotechnology, 2003). 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). 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).

Gene flow is further complicated because pollen and seeds are dispersed differently depending on plant species and growing environment. 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 have begun studies to determine the extent of pollen drift in corn, wheat and sunflower. Pollen studies in corn are most advanced; the goal is to develop a predictive model of corn pollen dispersal under a range of Colorado growing conditions.

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).

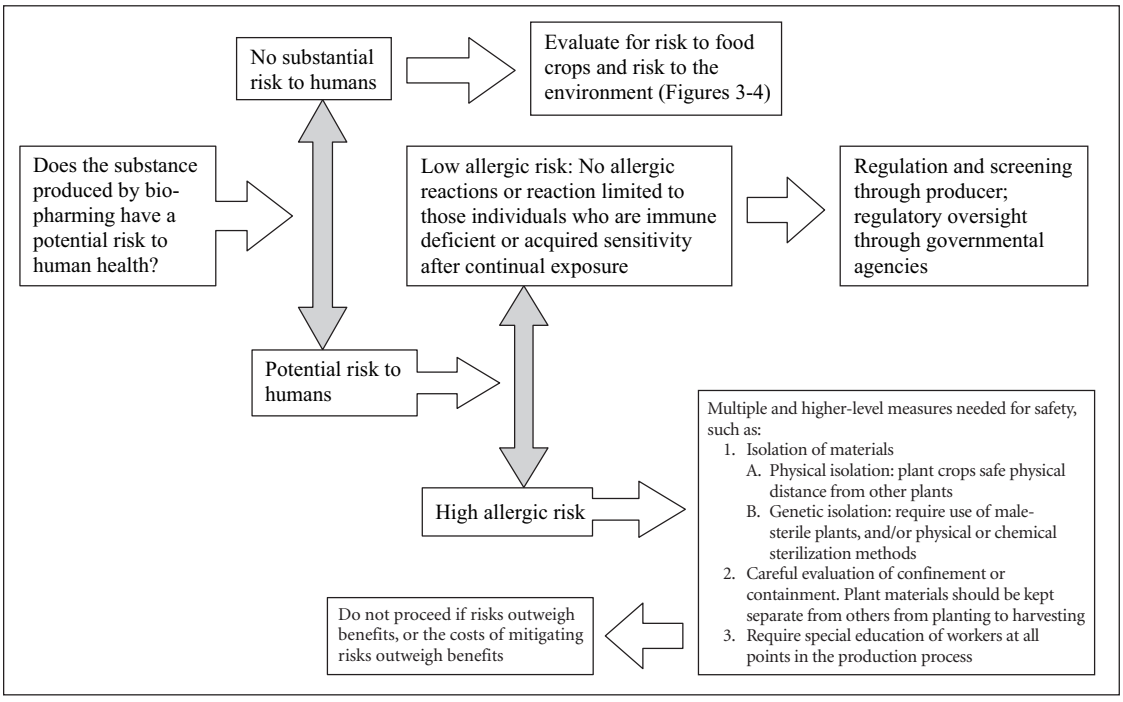
In 2000, StarLink™ corn,[1] a genetically engineered variety that had not been approved for human consumption, was detected in a wide array of corn-based food products in the supply chain. In an incident in November 2002, federal inspectors announced they had detected bio-pharm corn mingled in commodity soybeans in Nebraska. The corn, genetically engineered by ProdiGene Inc. to produce proteins for a pig vaccine, was harvested along with soybeans apparently because seed remained in the field after the bio-pharm crop had been harvested. The "volunteer" corn plants sprouted among soybeans in the same field the following season and, in violation of U.S. Department of Agriculture regulations, were not removed. There was no evidence of allergic reaction among consumers in the StarLink case, and USDA officials determined that the ProdiGene commingling posed no safety risks for consumers. Even so, the cases had significant economic consequences for domestic and international commodities markets (Taylor and Tick, 2001; U.S. Department of Agriculture, 2002; Zinnen, 2002; Fox, 2003; "ProdiGene fined," 2003).

Research demonstrates 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 the human food or livestock feed chains. What, then, are the implications – or risks – of unintended flow and mingle involving crops with novel traits? 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. The National Research Council recommends that bio-pharming risks be assessed on a case-by-case basis with consideration for the crop, genetically engineered trait and growing environment (National Research Council, 2002). The following frameworks (See Figures 2-4) are intended to identify potential risks associated with each bio-pharming proposal, as well as possible ways to mitigate those risks.

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

Figure 2: Does the plant-made protein pose potential risks to human health?*

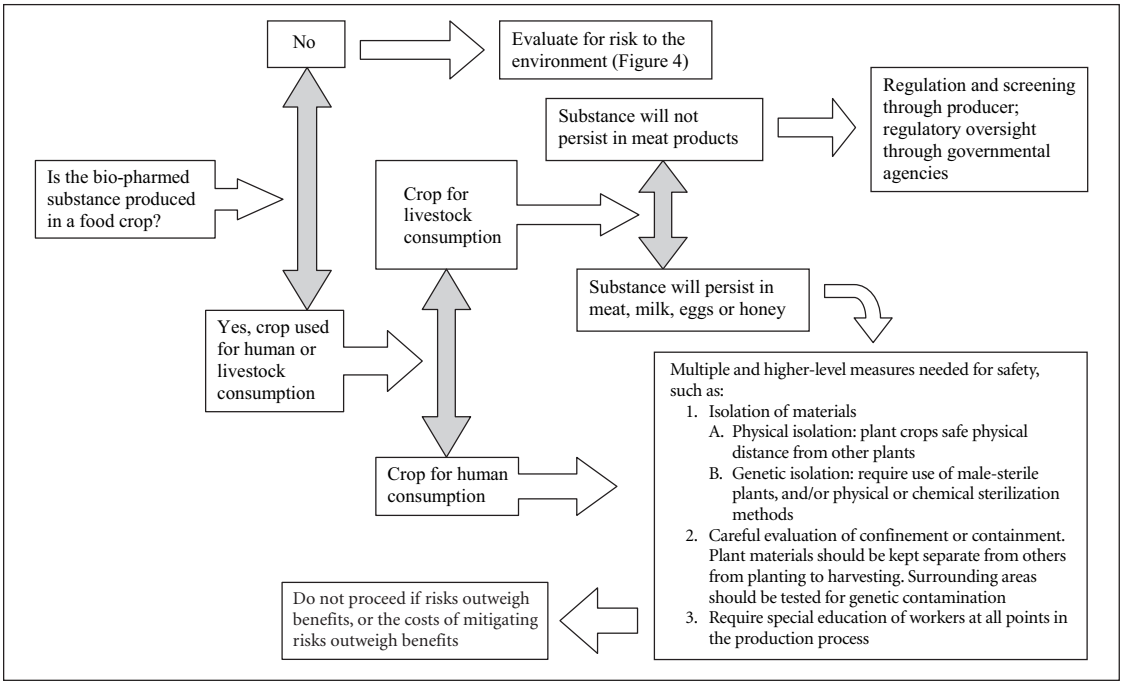
This framework addresses human-health risks and includes risk assessment for occupational exposure, meaning the potential risks to workers involved in producing and processing bio-pharm material.



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

Figure 3: Is the plant-made protein produced in a food crop?*

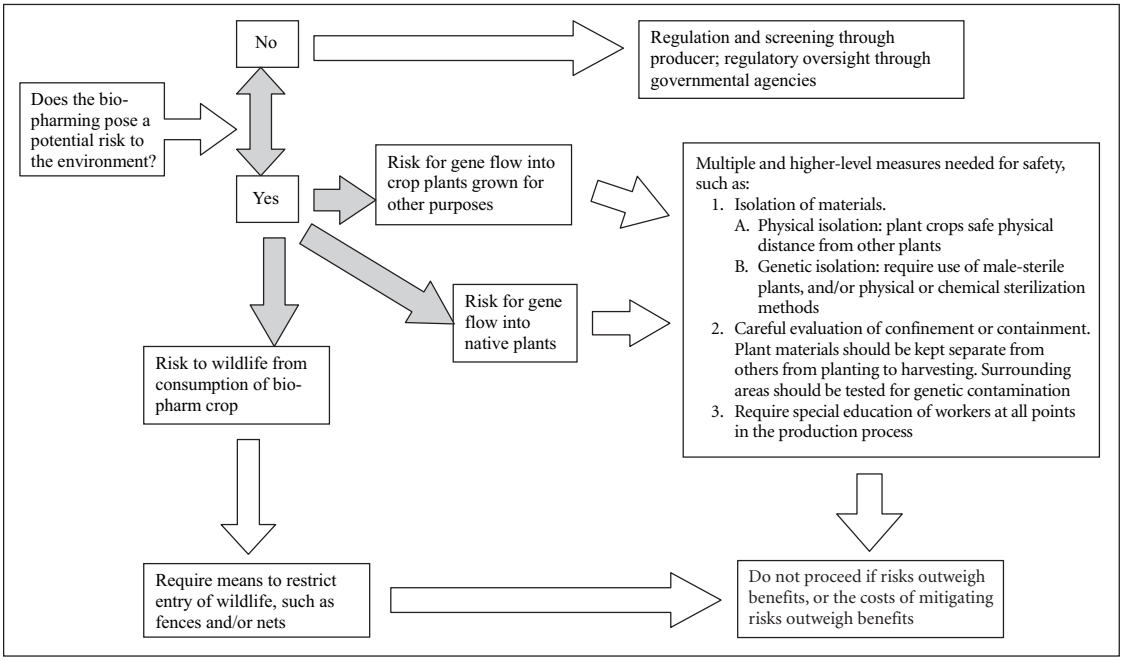
This framework considers risk assessment for unintentional bio-pharm impacts on food and feed supplies. For purposes here, "food crop" means a plant whose products are directly or indirectly consumed by humans or livestock for nutrition.



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

Figure 4: 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.

Why might stakeholders be involved?

Colorado decision makers might consider involving stakeholders when determining how to proceed with bio-pharming. This paper defines stakeholders as Colorado residents interested in and potentially affected by bio-pharming, including farmers, economic-development experts, agricultural businesspeople, university researchers, and members of consumer, environmental and agricultural organizations.

State residents, by offering questions, insights and opinions, could assist decision makers in important ways:

- Stakeholders, particularly community residents, can help determine the significance or acceptability of established bio-pharm benefits and risks (Rollin, 1996; Ellstrand, 2003b).
- Stakeholders can help decision makers anticipate, understand and address economic, ecological, political and other issues related to bio-pharming.
- Stakeholder involvement is a key step in improving public understanding of bio-pharming.

Participants in four community focus groups held by the Colorado Institute of Public Policy voiced interest in and concern about bio-pharming; they demonstrated ways that Colorado stakeholders might contribute to bio-pharm decision-making. Attendees discussed:

- Issues related to gene flow and commingling;

- Their desire for more information about bio-pharming, preferably based on independently conducted research; and
- How economic development could occur in Colorado through integrated bio-pharm crop cultivation, processing and related activity, all under appropriate safeguards.

How is bio-pharming regulated?

Two federal agencies and one state agency currently regulate different aspects of bio-pharming:

- The U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) considers permit applications from entities seeking to grow bio-pharm crops, grants approval or denies field tests, and dictates cultivation practices meant to minimize risks. Bio-pharm crop production requires annual approval, called "perpetual permitting."
- The Food and Drug Administration (FDA), which is charged with ensuring the safety and efficacy of drugs, grants approval for human clinical trials and marketing of plant-made pharmaceuticals. The FDA also oversees manufacturing procedures to guarantee product quality and potency.
- The Colorado Department of Agriculture may review APHIS assessments of permit applications and may recommend additional safety measures.

Federal bio-pharm regulations are undergoing review, and USDA officials have stated their intent to update policies and protocols that govern bio-pharming (USDA, 2004).

Under current regulations, the state Department of Agriculture may review bio-pharm cultivation applications after they have undergone preliminary assessment by APHIS. However, APHIS can legally issue a bio-pharm permit even if a state agriculture department does not concur; APHIS is not obligated to add permit provisions suggested by state departments of agriculture. This regulatory approach suggests that the current bio-pharm permitting process might not fully account for state-based knowledge of local growing conditions, stakeholder concerns, community infrastructure and other issues potentially important to bio-pharm production. Yet there might be a policy window to effect change: Federal regulators have expressed interest in working with states to address concerns about bio-pharm permit applications. And many states are using legislation to stake out their roles in bio-pharming (Pew Initiative on Food and Biotechnology, 2004).

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.

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