

Biopharming and the Food System: Examining the Potential Benefits and Risks

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Biopharming (using crops as drug-producing bioreactors) offers tremendous economic and health benefits stimulated by improving biotechnology methods. However, these benefits must be weighed against the potential risks to the food supply system and the costs of containing pharma crops to meet zero-tolerance contamination requirements. A combination of strong and adaptable regulatory oversight with technological innovations is required to achieve the twin goals of capturing the benefits of biopharming and safeguarding the food system and the environment. This paper examines the demand pull driving biopharming and the risk and liabilities to agriculture and reviews the regulatory and technological responses to the containment challenge faced by the food industry.

Key words: biopharming, biotechnology regulations, drug development, food system, plant-made pharmaceuticals, transgenic crops.

Introduction

Advances in genetic engineering now make it possible to use crops such as corn and tobacco as drug factories. Plants used as bioreactors (*biopharming*) may soon represent one of the most important developments in US agriculture, as pharmaceutical and chemical industries use field crops to produce therapeutic proteins, drugs, and vaccines. Pharmaceutical crops represent a radical departure from the traditional idea of crops as a source of food, feed, and fiber. The main driver for pharmaceutical crops comes from the biotech and pharmaceutical industry, where there is a growing recognition of the vast economic potential of using plants as platforms for drugs and therapeutic compounds. However, biopharming also presents unique challenges for the food and agricultural sector and federal regulators. The challenge arises from the strict requirement—enforced by federal regulations—that plants grown for pharmaceutical and industrial compounds (not approved for food and feed use) must stay clear of the food system under a zero-tolerance standard. The key issue is whether the economic payoffs from growing pharmaceutical plants outweigh the costs associated with the risk of food system contamination.

The objectives of this article are to examine the demand forces from the biotech industry behind biopharming and to assess the implications for food and agriculture (i.e., the risks associated with growing these crops in open fields). The paper also addresses the regulatory and technological responses to maximize containment effectiveness and minimize contamination risks.

Drug Developments and the Appeal of Plant-Made Pharmaceuticals

The drug development process within the pharmaceutical industry has experienced a significant transformation over the last two decades, driven largely by biotechnology advances. Biotechnology played a key role in the expansion of large-molecule drugs (as opposed to the small-molecule drugs manufactured by chemical synthesis). Moreover, biotechnology further stimulated the trend toward biological sources for drugs and therapeutics. These drugs, known as biologics, include any protein, virus, therapeutic serum, vaccine, and blood component. Another major impact of biotechnology was to enable the industry to move beyond simple replication of human proteins (such as insulin or growth hormones). Rather, new biopharmaceuticals are genetically engineered proteins targeting some of the major illnesses in industrial countries, such as cancer, cardiovascular, and infectious diseases—all critical to an expanding aging population.

In the last two decades, there has been an unprecedented interest in proteins and antibodies (as opposed to the traditional small-molecule drugs) stemming from their potential to tackle a whole array of new diseases that have not been addressed by small-molecule drugs. An advantage of these large-scale molecule drugs is their ability to target diseases in a very specific manner, thus maximizing efficacy while minimizing side effects. Hence, the market share of biologic-derived drugs has been growing at a much higher rate because of their perceived safety and effectiveness. For an industry that reached \$430 billion of global drug sales, the average

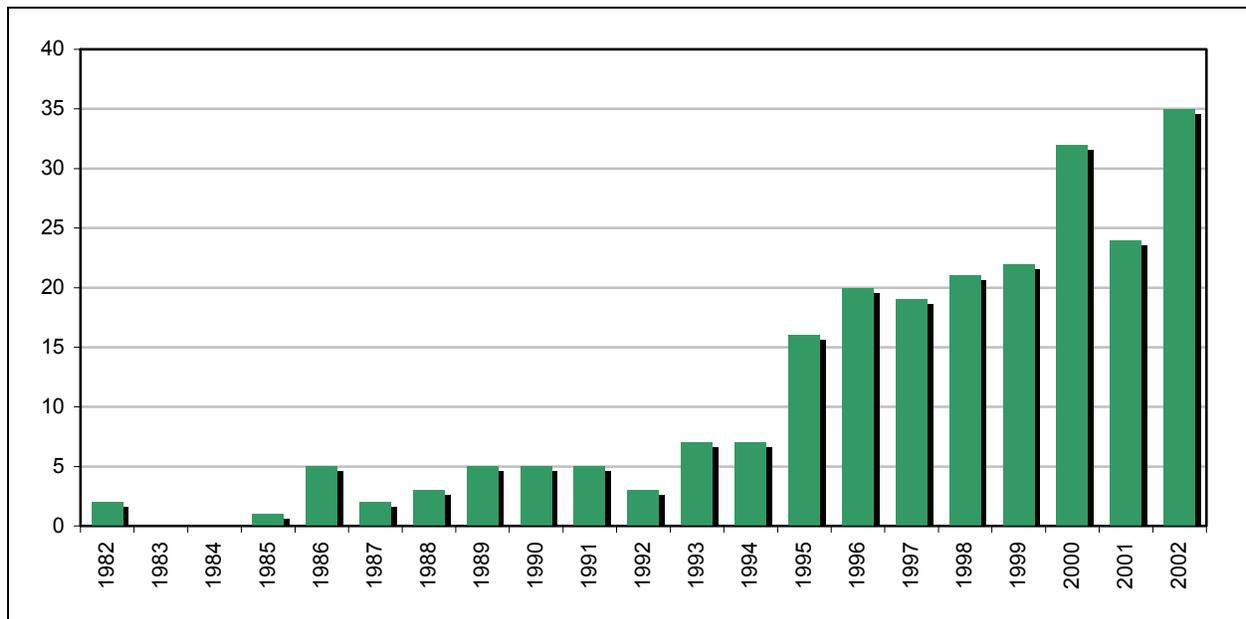


Figure 1. Number of new biotech drugs and vaccines approved.

Note. Data from Biotechnology Industry Organization (2002).

industry growth of small-molecule drugs is around 7–8% over the next decade, compared to the 15% growth rate for the therapeutic protein segment over the same period (IMS Health, 2003).

Building on developments in genetic engineering since the mid-1970s, the biopharmaceutical era truly began in early 1980s, starting with the release of the first transgenic drug, insulin, in 1982. Since then, biotechnology has had a threefold impact on the manufacture of therapeutic proteins, which makes up a significant segment of all biologically-derived drugs. There are currently 84 biopharmaceuticals on the market serving 60 million patients worldwide for a cumulative market value of \$20 billion (Biotechnology Industry Organization, 2004; Figure 1).

According to the Pharmaceutical Research Medical Association (2003), 500 biopharmaceuticals are estimated to be in clinical trials globally, 378 of which are in earlier stages (Phase I and II), while 122 are in Phase III or awaiting FDA approval (Figure 2). Using historical trends for drug approval rates, industry analysts expect an average of six or seven new large-molecule drugs to reach the market each year over the next several years (Ginsberg, Bhatia, & McMinn, 2002). These monoclonal antibodies, which require a large production capacity, are expected to make up about a third of all new therapeutics. Building on recent successes and drug approvals, the strong biotech therapeutics pipeline is creating a serious supply shortage for drug manufactur-

ing and inducing extended market disequilibrium, where demand far outstrips supply.

Large-molecule therapeutics, which cannot be produced by chemical synthesis, are traditionally manufactured either through microbial fermentation or more commonly via mammalian cell culture. However, it is expected that current cell culture facilities are unlikely to meet expected demand. There is already a supply capacity crunch resulting from recently approved monoclonal antibodies, which are primarily used for chronic diseases that often require high dosages. These new drugs have stretched the fermentation production to full capacity. Moreover, this supply-demand imbalance is expected to get worse in the future, as more biotech therapeutics are approved. For example, each newly approved monoclonal antibody requires 100,000 kg of production annually requiring new fermentation capacity to be built. To meet the expected demand for new drug production, more than three times the current production capacity may be required. It is estimated that 20–50% of potential therapeutics industrywide could be delayed due to the lack of manufacturing capacity (Fernandez, Crawford, & Hefferan, 2002).

A striking example of the drug supply shortage is the case of Enbrel—a biotech drug, introduced by Immunex in 1998, that proved to be highly successful for treating rheumatoid arthritis, which affects two million patients in the United States. Enbrel is produced in 10,000-liter bioreactors of cultured Chinese hamster cells; its suc-

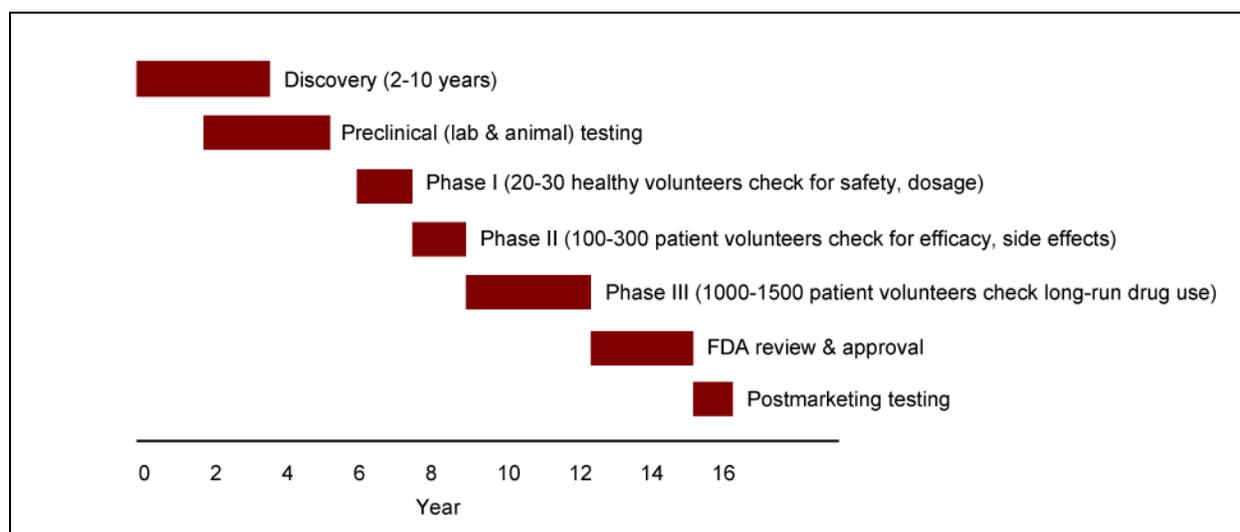


Figure 2. Biotech drug discovery process.

Note. Data from Pharmaceutical Research Medical Association (2003).

cess created a supply shortage starting in 2001. By March 2002, there was a waiting list of 13,000 patients. In response, Immunex began rationing to pharmacies with the goal of maximizing the number of treated patients. At the same time, Immunex launched a new production facility in Germany, which will take up to five years to build and approve at a cost of \$450 million. Meanwhile, the supply shortage is expected to continue into the near future.

The Appeal of Plant-Made Pharmaceuticals

The current interest in pharmaceutical plants can be viewed both as a response to these supply shortages and as an alternative platform to develop therapeutics. Although many drug companies are pursuing additional fermentation capacity to stave off the manufacturing crunch, other drug and biotech firms are giving serious consideration to alternative platforms, including transgenic plants and animals, insect cells, and even yeast cultures (Table 1). Of these, plant-made pharmaceuticals (PMPs) offer many advantages over mammalian cell culture methods. First, there is the cost advantage. Industry estimates of unit costs of therapeutic production with animal cell bioreactors range from as low as \$106/g of antibody to \$650/g (Morrow, 2002). The cost of producing the same amount of therapeutics from plants is estimated to be four to five times lower than the mammalian cell culture method. As an illustration, the production of 500 kg of monoclonal antibodies would require an investment of US\$450 million for a mammalian cell culture fermentation facility and four to seven

years to build and approve. By contrast, the same amount of monoclonal antibodies could be produced on 500 acres of corn using a purification facility costing US\$80 million and three to five years to build and approve. The per-unit (gram) cost is \$350–1,200/g (depending on scale) for mammalian cell culture versus \$80–250/g using pharmaceutical corn (depending on scale; Fernandez et al., 2002).

A second advantage of PMPs is the large production capacity offered by plants—in particular production scalability, which requires only that new seeds be developed and that more acres be brought into production to meet additional demand. A third advantage of PMPs is they are believed to be inherently safer than recombinant proteins from microorganisms or cells. PMPs do not carry potentially harmful human or animal viruses into the drug—a possible limitation for drugs derived from mammalian cell cultures or animal milk.

Plant-Made Pharmaceuticals and Biopharming: An Emerging Industry

The technology for producing pharmaceuticals from plants has been available for more than 16 years. The genetic engineering technology, referred to as the *Polymerase Chain Reaction* (PCR), makes it possible to isolate the DNA sequence that codes for a particular protein, reproduce many copies of that sequence, and ultimately produce considerably larger quantities of particular proteins (Hill, 1999). The process of developing and using plants to produce pharmaceutical compounds consists of identifying the target protein and then identi-

Table 1. A comparison of pharmaceutical expression systems.

Expression system	Advantages	Disadvantages	Applications	Cost per gram
Bacteria	Established regulatory track; well-understood genetics; cheap and easy to grow	Proteins not usually secreted; contain endotoxins; no posttranslational modifications	Insulin (<i>E. coli</i> ; Eli Lilly); growth hormone (Genentech); growth factor; interferon	
Yeast	Recognized as "safe;" long history of use; fast; inexpensive; posttranslational modifications	Overglycosylation can ruin bioactivity; safety; potency; clearance; contains immunogens/antigens	Beer fermentation; recombinant vaccines; hepatitis B viral vaccine; human insulin	\$50–100
Insect cells	Posttranslational modifications; properly folded proteins; fairly high expression levels	Minimal regulatory track; slow growth; expensive media; baculovirus infection (extra step); mammalian virus can infect cells	Relatively new medium; Novavax produces virus-like particles	
Mammalian cells	Usually fold proteins properly; correct posttranslation modifications; good regulatory track record; only choice for largest proteins	Expensive media; slow growth; may contain allergens/contaminants; complicated purification	Tissue plasminogen activator; factor VIII (glycoprotein); monoclonal antibodies (Herceptin)	\$500–5,000
Transgenic animals	Complex protein processing; very high expression levels; easy scale up; low-cost production	Little regulatory experience; potential for viral contamination; long time scales; isolation/GMPs on the farm	Lipase (sheep, rabbits; PPL Therapeutics); growth hormone (goats; Genzyme); factor VIII (cattle)	\$20–50
Transgenic plants	Shorter development cycles; easy seed storage/scaling; good expression levels; no plant viruses known to infect humans	Potential for new contaminants (soil fungi, bacteria, pesticides); posttranslational modifications; contains possible allergens	Cholera vaccine (tobacco; Chlorogen, Inc.); gastric lipase (corn; Meristem); hepatitis B (potatoes; Boyce Thompson)	\$10–20

Note. Data from BioPharm International (2003).

fyng and isolating the gene that codes for the protein. One approach is to insert the gene into a plant vector, which enables transfer of new DNA into plant cell. Alternative approaches use electrical discharge or biolistic particle bombardment to insert the gene into the plant cell. Plant cells are then grown into callus and then into seed-producing plants. The seeds are grown in a greenhouse or field, and the protein is purified from leaf or seed material.

There are more than 20 biotech organizations that specialize in PMPs. Many of these organizations (companies or universities) have specialized in one (or more) crop of choice as a platform for therapeutic production. Table 2 lists several of the organizations currently active in PMP research and development. Among these is the Missouri-based Chlorogen, Inc., which specializes in developing PMPs expressed in tobacco, including vaccine for cholera, human serum albumin, and interferon for hepatitis C, among others. Ventria Bioscience (California) uses rice to develop PMPs such as lactoferrin and lysozyme—proteins used for human and animal health applications. Meristem Therapeutics (France) uses corn to produce gastric lipase (for treating of cystic fibrosis) and uses gene-modified alfalfa to produce

albumin (used in heart surgery). Another firm, Medicago (Canada), has specialized in transgenic alfalfa to mass-produce hemoglobin for the growing blood-bank market. Large Scale Biology Corp. (LSBC) uses the tobacco plant to produce aprotinin (protease inhibitor), which is traditionally extracted from cow lungs. Few of these protein therapeutics have yet to reach commercial stage; many are at various stages of development and clinical testing, ranging from preclinical stages to advanced or Phase III clinical stage levels.

Field testing of the pharmaceutical (and industrial) crops in the United States has been taking place since the early 1990s. However, the pace and number of these field-test trials have accelerated in recent years. According to APHIS data, more than 325 sites of field trials in the United States were approved from 1991 to 2004 for pharmaceutical, novel protein, and industrial enzymes (Table 3). The number of these trials has grown in the past few years, particularly in corn, tobacco, soybeans, and rice. Although corn has dominated as the crop of choice, there has been some drop in corn trials since 2003 as a result of a move toward nonfood crops for pharmaceutical trials.

Table 2. Selected North American and European biotech companies specializing in plant-made pharmaceuticals.

Biotech company	Crop used	Target plant-made pharmaceuticals
Ventria Bioscience (California)	Rice	Lactoferrin and lysozyme
Chlorogen, Inc. (Missouri)	Tobacco	Cholera vaccine; human serum albumin; interferon (hepatitis C)
Medicago (Canada)	Alfalfa	Hemoglobin
Meristem (France)	Corn; tobacco; alfalfa	Hemoglobin; gastric lipase (cystic fibrosis, pancreatitis; Phase II); albumin (surgery); cancer therapeutic antibodies
MPB Cologne (Germany)	Potato; rapeseed	Antibody for detection of food/water borne pathogens
SemBio Systems (Canada)	Safflower	Antiobesity peptid; somatotropein
EpiCyte (USA)	Corn	Monoclonal antibodies (plantibodies); EPI-19 (bronchionliotis/ pneumonia in infants)
Large Scale Biology Corp.	Tobacco	B-cell non-Hodgkin's lymphoma (Phase III); alpha-galactosidase A (therapy for Fabry's disease); patient-specific cancer vaccines
Plant Biotechnology (California)		CaroRx (targets bacterium that causes tooth decay)
Cornell University	Potato	Edible vaccine for Hepatitis B
AltaGen (USA)	Potato	Hemoglobin; factor VIII; human growth hormone

Table 3. Number of field testing permits by APHIS as pharmaceutical, industrial, or novel traits (1991–2004 cumulative).

	Industrial enzymes	Novel proteins	Pharma plants	Total	%
Corn	11	157	63	231	71.1
Soybeans	10	4	16	30	9.2
Alfalfa	2	1	1	4	1.2
Barley		1	1	2	0.6
Rapeseed	2		1	3	0.9
Tobacco		1	14	15	4.6
Tomato			1	1	0.3
Rice	1	2	8	11	3.4
Safflower	1	2		3	0.9
Wheat		2		2	0.6
Sugarcane			1	1	0.3
Other	5	6	11	22	6.8

Note. Data from Information Systems for Biotechnology (2005).

Open-Field Cultivation of Pharma Crops: The Containment Challenge

Genetically engineered crops grown to produce PMPs have little in common with traditional agriculture. These pharmaceutical crops do not represent a new wave of value-added agriculture. Rather, these crops represent open-air bioreactor farming, a component of pharmaceutical and industrial enzyme manufacturing process. Their cultivation in the field is predicated on the requirement of total isolation and confinement from the food supply. The cost structure of pharmaceutical crops is determined mostly by risk minimization requiring (a) sophisticated risk management to avoid potential gene

outflow and minimize impact on nontarget organisms as well as workers' health; (b) identity preservation based on a tight closed-loop system to avoid any possibility of commingling with food supply; and (c) a set of quality-control procedures with a tight chain of custody to satisfy the isolation and confinement requirement.

Genetically engineered pharmaceutical-producing crops require a permit from the United States Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS), which must include a containment plan for the plants during the production, handling, and movement of plants in and out of the field. APHIS reviews all plans for seed production, timing of pollination, harvest, crop destruction, shipment, confinement, and the storage and use of equipment. Field inspections may take place up to five times during the growing season coinciding with critical times of production. APHIS issues a field test permit either to an individual company or research institution who, in turn, may subcontract with growers. Subcontracting farmers are also required to undergo training in permit requirements and implementation.

The field confinement measures for pharmaceutical crops vary depending on the biology of the plant. Self-pollinating crops (e.g., rice, barley), with their heavy pollen, have isolation distances of 50 to several hundred feet. Isolation for corn, with its wind-borne, relatively light pollen, is at least one mile. Confinement guidelines also require a 50-foot fallow zone around pharma corn. There is also a restriction on growing a food or feed crop on the same field the following year. Pharma corn grown between one half and one mile must be planted at least 28 days before or after any other corn within this distance. (This *temporal isolation* minimizes the likeli-

hood of pollen shed overlap and cross-fertilization.) In addition to mandatory training for personnel, the use of dedicated equipment for planting and harvesting must be approved by APHIS along with dedicated facilities for storage of equipment and regulated articles during the season.

The FDA also has domain over human drug and biological products produced from pharmaceutical plants. The FDA considers pharmaceutical crops to be outdoor manufacture sites and subject to regulatory scrutiny analogous to that applied to conventional drug manufacturing facilities. The manufacturing process, including field production, must follow the current Good Manufacturing Procedures (GMP) to oversee greenhouse or field production practices. Basically, the FDA expanded the GMP (traditionally applied to manufacturing facilities) to the wide-open field for pharmaceutical crops. The aim is to insure consistent manufacturing processes and product safety, purity, and potency. Prior to commercial production of PMPs, the FDA must decide favorably on the safety and efficacy of the pharmaceutical product, based upon clinical tests, chemistry manufacturing and control, pharmacology/toxicology information, and an acceptable inspection of the manufacturing facility.

Overall, the FDA's responsibility extends to the entire manufacture of the biopharmaceuticals—from production to waste streams—so its role necessarily complements and overlaps the role of APHIS at the field production stage. Whereas APHIS regulates the growing and isolation of engineered crops, the FDA regulates materials, equipment, and manufacturing processes—encompassing everything from seed stock to packaging.

Federal regulatory rules are constantly evolving in response to advances in science and technology. These standards have recently been revised (*Federal Register*, March 6, 2003). Moreover, APHIS amended its regulations for genetically engineered plants that make drugs and industrial compounds, requiring a standard permit for field testing rather than notification (essentially an expedited permit) as previously allowed. In 2004, APHIS issued a public notice for proposed rule changes to its biotechnology regulations (*Federal Register*, January 23, 2004). The proposed revisions would define specific-risk-based categories for field testing for pharmaceutical and industrial crops and consideration of environmental assessments in the issuance of field-test permits. At the same time, both APHIS and FDA are reviewing additional revisions, including specifying appropriate training standards the use of third-party auditors and standard-setting organizations.

Biopharming and the Food Industry

Given the potential risks and liabilities associated with accidental commingling with the food supply, and facing the daunting task of ensuring near-100% containment, the food and the biotech industries have taken a precautionary approach to pharmaceutical crops and support for risk-based regulations. The Prodigene incident case in 2002 illustrates the type of risks facing the food industry. In Nebraska, during the 2002 growing season, APHIS inspectors discovered “pharmaceutical” volunteer corn growing in a soybean field. The corn was from the previous year, when Prodigene had tested a pharmaceutical corn to produce a swine vaccine. As a result, both the harvested soybeans (500 bushels) and the entire soybean load of 500,000 bushels in local elevator were quarantined. In another accident in Iowa, the USDA forced Prodigene to burn 155 acres of conventional corn that may have cross-pollinated with some of the company's pharmaceutical plants. In both cases, the infraction was viewed to come from Prodigene's failure to adhere to permit protocols issued by APHIS. Prodigene was fined US\$250,000 and required to pay approximately \$3 million for the cleanup costs and disposal of contaminated corn and soybeans.

Although the quick discovery and resolution of the Prodigene incidence was credited to the effectiveness of the existing regulations and oversight, the incidents themselves provided the industry with a precedent for what could happen in the future as more pharmaceutical crops are grown in open fields. It is generally agreed that a 100% guarantee of zero contamination may be an impossible goal to achieve under field growing conditions. This presents the food industry with several challenges requiring consensual responses. More immediately, a coalition of food industries seems to favor the inclusion of food-safety assessment by event prior to issuing a permit. An implication of such an approach is a better handle on risk in case the containment fails. In practice, such an approach would tilt the current research and development away from food crops (such as corn) in favor of nonfood crops (tobacco). This may explain, in part, the drop in the number of pharmaceutical corn field trials, beginning in 2003, and the concurrent rise of tobacco field trials.

In the medium and long term, improved confinement methods may require new and innovative responses from the biotechnology industry itself. Many biotech companies are currently pursuing production strategies that combine both greenhouses and confined facilities with open fields. Other firms use plants in completely

closed facilities or greenhouses. An example is Medicago, which grows biopharmaceutical alfalfa for therapeutic proteins in greenhouses. Under this system, the company can produce up to 9 kg/year of protein with a unit value of \$10,000 per gram of protein using one 1,300-square-foot greenhouse (Zavon & Flinn, 2003).

However, when large quantities of pharmaceutical products are required or the crops do not grow well in isolated systems, open-field production is necessary. This tends to favor self-pollinated crops (e.g., soybeans, rice, or barley) at the expense of open-pollinated crops (corn). There are other technology-based options to ensure confinement. Among possible solutions is the use of pharma plants with a “terminator gene” to ensure plant sterility or engineering plants with visual markers for easy identification. For wind-pollinated crops like corn, a precautionary practice currently in use is to manually detassel corn (i.e., remove male flowers) and to plant rows of nontransgenic corn to supply pollen for pharmaceutical plant and avoid pollen drift beyond the pharma field. The preferred option from the food industry perspective is the cultivation of pharma crops in locations that are far removed from areas where food crops are grown, including possibly sourcing overseas.

Biopharming and Environmental Impact: Technological Solutions

Pharmaceutical crops may also present risks to the environment which include potential safety issues linked to contamination with residual pesticides, herbicides, and toxic plant metabolites. An additional concern is an altered plant contaminating wild strains and human exposure to plant material containing potent drugs. There is also the concern that transgenes will spread in the environment and affect nontarget organisms. However, not all biopharmaceuticals may be harmful, and many may be considered benign to nontarget organisms. This is because many biopharmaceuticals are proteins with little or no biological activity when ingested (e.g., vaccines and antibodies). Moreover, most proteins are digestible and may pose little hazard of toxicity. Nevertheless, biopharmaceuticals may be toxic in higher doses (e.g., anticoagulants, hormones, and enzymes) or may persist longer in the environment (as in the case of lipophilic drugs).

To limit environmental exposure, several technological solutions are being pursued. One solution is to induce genes to produce therapeutic proteins only after harvest. For example, to induce production of the protein glucocerebrosidase, LSBC uses a nontransgenic

tobacco plant cut at a given height and sprayed under confined conditions with recombinant plant virus. An alternative LSBC practice involves spraying tobacco plants in the field, harvesting a few days later, and then purifying the protein (Zavon & Flinn, 2003). Another solution is to use chloroplast transformation to limit gene flow. This approach consists of introducing the gene not in the plant genome per se but rather in chloroplast DNA, which enables the plant to produce the target protein but is not transmitted to the seed. This is the approach followed by Chlorogen for tobacco. Yet another option is to use plant genomes that are incompatible with nearby related species.

Conclusions

Plant-made pharmaceuticals represent a significant development in the ongoing biotechnology revolution. But are they inevitable? Certainly pharmaceutical crops’ lower production and capital costs and their greater production flexibility give them a strong appeal as biofactories for drug development. However, many scientific, regulatory, and economic hurdles remain. First, as a new technology, PMPs have yet to fully demonstrate “proof of concept”; the suitability of green plants for protein manufacture is still not fully resolved. Although the economics seem compelling, and all the trends so far point toward feasibility, until these are approved by the FDA for commercial use, there is still a large segment within the drug industry that is not yet convinced that plant proteins will be as effective as animal-based proteins. A second obstacle may come from new technological developments, which may or may not continue to favor open-field cultivation compared to confined greenhouse production. A third obstacle is that the cost advantage of PMPs could change in favor of other production (expression) platforms with technological improvements in fermentation processing or with animal-based transgenics (such as the use of milk glands as the production medium).

Realistically, plants need to be viewed as just one possibility among many for manufacturing therapeutic proteins. PMPs could evolve along several paths. They could either dominate specific therapeutic protein markets or monopolize biogenics. Overall, plant transgenics will likely be the favorite expression system with proteins that do not express well in traditional systems, are given in large doses, or for which production costs make them too expensive to bring to market.

Pharmaceutical crops may not require large amounts of acreage. The area needed will depend on the potential

demand for the pharmaceutical products. For example, the production of the antibody against bacteria that cause tooth decay would require 600 kilograms per year, which can be supplied by a single large tobacco farm. On the other hand, using tobacco to produce human serum albumin may require up to 45,000 acres of tobacco to meet world demand. However, for pharma crops grown in open-field conditions in proximity to food crops, the challenge of insuring 100% containment will be daunting. Consequently, one can expect significant spillover effects on food-crop markets, in the likelihood of contamination, particularly if PMPs are expressed via food crops such as corn or rice.

For the biotech and drug industry, biopharming offers tremendous economic and health benefits once the current cycle of product development reaches the commercialization stage. However, for these benefits to be fully realized, the central issue of risk to the food industry and the environment is a critical requirement. Industrial and agricultural investments in biopharming must weigh the size of economic payoffs from growing pharmaceuticals against the costs and liabilities within the food supply system, including the potential loss to export markets. A combination of strong and adaptable regulatory oversight with technological solutions are required if the twin goals of realizing the full potential of biopharming and safeguarding the food system and the environment are to be met.

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