

PLANT-MADE PHARMACEUTICALS

Financial Risk Profile

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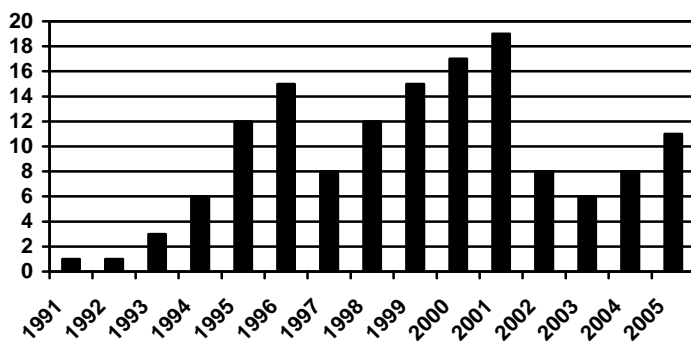
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SUMMARY

- While the biopharmaceutical industry as a whole has had some limited success, attempts to employ genetically engineered plants as a production platform for “plant-made pharmaceuticals” (PMPs) have foundered despite 15 years’ of field trials and huge infusions of capital.
- Companies have failed to bring even one PMP through the FDA’s drug approval process due to technical difficulties unique to the plant-based system – immunological issues, problematic extraction of the drug from plant tissue, and inconsistency in drug quality and yield in differing environments.
- The \$500 billion food industry has lobbied against the use of food crops for PMP production, fearing contamination of the food supply. Food companies and federal regulators insist on a “zero tolerance” standard with respect to contamination that scientists agree is impossible to achieve on a commercial scale. Without tolerances, outdoor PMP producers face extraordinary liability for contamination at all levels of the food chain.
- Food industry pressure has also resulted in stricter, more costly government regulation. USDA imposed a costly settlement on then industry leader ProdiGene, Inc. for violations that led to two high-profile contamination incidents involving the company’s pharmaceutical-producing corn in 2002.
- Insurers are increasingly leery of insuring agricultural biotech as a whole; they will be even less likely to provide coverage for PMP producers.
- Four major biotech companies are leery of PMPs. Industry leader Monsanto (MON) closed its PMP subsidiary Integrated Protein Technologies in October 2003. Novartis Pharma, a major biopharmaceutical producer, is skeptical of the GE plant platform and recently committed \$6 billion to further development of traditional fermentation systems.
- Smaller players that concentrate on PMP production have gone bankrupt (CropTech & Large Scale Biology, tobacco). Epicyte Pharmaceutical, once a leader in pharma corn development, also went bankrupt and was taken over by Biolex in April 2004; Biolex utilizes the aquatic plant duckweed to make experimental biopharmaceuticals in contained and controlled bioprocessing facilities.
- Two National Academy of Sciences’ committees have criticized the use of food crops for PMP production due to concerns that PMP contamination of foods could pose health risks.
- Farming and public interest groups increasingly oppose open-air biopharming. Farmer-led opposition killed field trials of pharma corn in Colorado in 2003 (Meristem Therapeutics) and pharma rice in California (2004) and Missouri (2005) (Ventria Bioscience).
- Contained and controlled alternatives to the open-air cultivation of drug-producing plants are gaining favor as opposition to biopharming grows.



Number of permits for field trials of pharma & industrial crops (1991 – 2005). See footnote 5 for details.

Company	Crops, No. of Permits, Notes
Monsanto	Corn, soybeans; 44 permits; shut down PMP operations in 2003
ProdiGene	Corn; 27 permits (none since 2002); taken over by Stine Seed
Ventria Bioscience	Rice, barley; 14 permits; failed bids to grow PMPs in CA & MO
Large Scale Biology	Viral-vectored tobacco; 11 permits; bankrupt 2005
CropTech	Tobacco; 7 permits; bankrupt 2003

Companies that have conducted the most outdoor pharma & industrial crop field tests (1991-2005)

INTRODUCTION

Biopharmaceuticals are proteins generated in living organisms that have medicinal properties. They were once obtained exclusively from animal or human tissues, such as insulin from pig pancreas or albumin from human blood. Although over 99% of biopharmaceuticals by weight are still obtained in this way from tissues,¹ there is a growing trend to produce biopharmaceuticals in fermentation facilities employing genetically engineered animal cells, bacteria, yeast or fungi. With over 132 brand name biotech products,² the global market in biopharmaceuticals was valued at \$32 billion in 2003.³

Genetically engineered (GE) plants represent an experimental platform for production of these compounds (i.e. “plant-made pharmaceuticals,” or PMPs). Factors driving the use of GE plants include anticipated reduction in production costs, ease of scalability, and storage cost savings vis-à-vis proven fermentation techniques.⁴ However, despite 15 years of open-air field experimentation and huge investments of time, money and scientific expertise, not a single PMP has passed FDA’s drug review process. PMPs are failing for numerous reasons, including technical difficulties, food industry opposition, increasingly stringent and costly regulation, untenable liability, opposition from farming and consumer groups, and growing interest in other production platforms.

MINIMAL INTEREST IN PMPs

Pharma and industrial crops represent only about 1.5% of overall U.S. field trials for transgenic crops. Experimental PMPs are grown primarily in GE corn, soybeans, tobacco and rice; outdoor plantings require permits from the USDA. According to USDA records, the number of authorizations issued for field trials of crops producing pharmaceutical and related compounds has fallen from a peak of 19 in 2001 to 6 in 2003, increasing to 11 in 2005 (see graph).⁵ While corn represents 47% of all pharma crop permits historically, pharma corn permits have fallen from a high of 13 in 2001 to just two in 2004 and one in 2005. Largely replacing corn are safflower, rice and especially tobacco. Over one-third of the pharma permits in 2004-2005 involved pharma tobacco, reflecting concern over contamination of food with PMPs.

TECHNICAL OBSTACLES

It has proven much more difficult than once imagined to produce human and animal

biopharmaceuticals in GE plants. The human immune system can react to a plant-made “human” drug as foreign due to subtle differences in structure between the natural and plant-made versions of the “same” compound. Immune system attack can render the drug ineffective, trigger allergic reactions or even cause auto-immune disorders. Another difficulty is extraction of the PMP from thousands of plant constituents without damaging it. Finally, the technique is plagued with inconsistency in drug yields and quality in plants with different genetic backgrounds, and in identical plants grown in different environments.⁶ For instance, inconsistency in plant-to-plant vaccine levels has undermined hopes of delivering “edible vaccines” in raw fruit or vegetable form.⁷

FOOD INDUSTRY HAS “ZERO TOLERANCE” FOR PMPs IN FOOD

Another important reason for declining interest in PMPs is the strong opposition of the \$500 billion food industry due to concerns about liability arising from contamination of the food supply with drugs. Geneticists and agronomists believe such contamination is inevitable at commercial scale – especially with corn, a prolific pollinator that has been the favorite PMP host plant.⁸ Thus, some have called for establishment of tolerances (i.e. maximum permissible levels) to legalize PMP contaminants in food.⁹ Yet the USDA and FDA maintain a zero tolerance standard for PMPs. And the food industry, normally supportive of liability-easing tolerances, has unequivocally opposed tolerances for PMPs, no doubt fearful of consumer and export market backlash upon discovery of even low “legal” levels of drugs in the food supply.¹⁰

Food company attitudes towards PMPs are shaped profoundly by the StarLink GE corn debacle, which cost them millions of dollars through food recalls, in part because the EPA held firm to a zero tolerance standard for transgenic residues of StarLink in food. With both the food industry and the government dead set against tolerances, open-air PMP production in food crops involves huge, and ultimately untenable, exposure to liability for PMP companies as well as farmers, millers, food companies, etc. Former Kraft Foods CEO Betsy Holden singled out the issue of PMP contamination of foods as a threat to her company and the food industry as a whole.¹¹

In 2005, Anheuser-Busch threatened to end all purchases of Missouri rice if Ventria Bioscience went forward with plans to grow its pharma rice in rice-growing southeastern Missouri.¹² The proposed

planting, which was also opposed by Missouri rice growers, never took place.

FOOD INDUSTRY DRIVES STRICTER, MORE COSTLY, REGULATION

In the fall of 2002, two high-profile contamination episodes catapulted “biopharming” onto CBS Evening News (11/13/02). The culprit was ProdiGene, Inc., a privately-held Texas firm that was once the leader in development of corn-based PMPs. One incident involved the USDA-mandated destruction of 500,000 bushels of contaminated soybeans in Nebraska and \$3.5 million in liability for ProdiGene. In a similar incident in Iowa, USDA ordered the destruction of 155 acres of field corn potentially contaminated with ProdiGene’s pharm variety via cross-pollination.¹³ Food companies and consumer groups outraged by these episodes lobbied the USDA for stricter regulation of PMP field trials, which came in early 2003 in the form of greater isolation distances, dedicated harvesting equipment and more inspections.¹⁴

Later in 2003, the USDA acknowledged 113 other violations by GE plant field trial operators, raising serious questions about the biotech industry’s ability and/or willingness to prevent contamination.¹⁵ In 2005, an internal audit of USDA’s performance at regulating GE and especially pharma crop field trials found numerous deficiencies, including failure to implement many of the measures supposedly enacted in 2003. USDA is unaware of the locations of many GE crop field trials, and in two cases, a total of 2 tons of pharmaceutical crops had been stored on-site for over one year without USDA’s knowledge or oversight.¹⁶

PMP PRODUCTION MAY BE UNINSURABLE

As part of the settlement imposed on ProdiGene for these violations, USDA is requiring the company to post a \$1 million bond before any more field trials to cover damages from any future contamination episode.¹⁷ The North American Millers’ Association demands that all PMP producers be required to obtain insurance coverage to indemnify everyone downstream in the food chain.¹⁸ But would insurers provide such coverage? According to Robert Hartwig, chief economist for the Insurance Information Institute: “Genetically engineered foods are among the riskiest of all possible insurance exposures that we have today.”¹⁹ The amount of coverage available to biotech firms in general has declined in recent years,²⁰ perhaps in

part due to a \$110 million settlement reimbursing *non*-StarLink growers for economic losses due to the StarLink corn contamination debacle.²¹ If insurance companies are increasingly leery of insuring even garden-variety GE crops, then their disinclination to cover companies whose operations threaten to put drugs and industrial chemicals in the food supply will be still greater.

BIG PLAYERS LEERY OF PMPs

Swiss-based Novartis Pharma, a global leader in biopharmaceuticals, is skeptical of the GE plant platform, and recently committed \$6 billion to further development of conventional fermentation systems.²² Ag biotech industry leader Monsanto (MON) announced closure of its biopharm subsidiary, Integrated Protein Technologies (IPT), in October 2003 due to “uncertainty of the longer-term reward from a highly capital-intensive business.”²³ DuPont (DD) and its subsidiary Pioneer currently have an internal policy to forego PMP development.²⁴ According to USDA data, neither Bayer CropScience (BAY) nor Syngenta (SYT) has conducted a single outdoor field trial of a drug-producing plant, though both companies have entered into joint ventures with biopharm dot.coms. Their strategy seems to be to avoid the financial risks associated with this unproven technique as well as the liability from potential contamination episodes while at the same time keeping some irons in the fire. Of the five largest ag biotech companies, only Dow Chemical (DOW) is pursuing PMPs, but by its own admission is having considerable technical difficulties with its plant-made monoclonal antibodies.²⁵

BIOPHARM DOT.COMS NOT DELIVERING

Efforts to develop PMPs are led by small firms such as ProdiGene, Epicyte, CropTech, Large Scale Biology and Ventria Bioscience. Despite \$6 million in subsidies from an Iowa state economic development fund, ProdiGene has delivered nothing to Iowa’s economy, and in fact was nearly sued by the Iowa Attorney General’s office for defrauding farmers with its “get rich quick with pharm crops” ploy.²⁶ ProdiGene, unable to pay USDA-imposed penalties (see above), was saved from bankruptcy through a no-interest loan from USDA and a buyout by Stine Seed Company.²⁷

In 2004, San Diego-based Epicyte Pharmaceutical, another pharma corn leader, shut down and sold its assets to Biolex of North Carolina. Epicyte’s closure is the latest in a series of San Diego biotech company failures, dashing the city’s

dream of becoming the ‘Silicon Valley of ag biotech.’²⁸ Epicyte’s collapse was due to technical difficulties in development of monoclonal antibodies and concern in the investment community about liability should the company’s pharmaceuticals contaminate the food supply. Significantly, Epicyte’s purchaser Biolex produces experimental monoclonal antibodies “in regulatory-compliant, contained and controlled bioprocessing facilities” utilizing the aquatic plant duckweed.²⁹

CropTech was a privately-held Virginia company once considered the leader in development of PMPs in tobacco. In the ten years of CropTech’s existence, it received over \$12 million in state and federal subsidies.³⁰ After failing to raise \$6 million from struggling VA tobacco growers to stay afloat, the company sought financing from North and South Carolina, but filed for bankruptcy before it could take advantage of South Carolina’s incentive package.³¹

California-based Large Scale Biology (LSBC), founded as Biosource Genetics in 1987, conducted the first outdoor field trial of a pharmaceutical-producing plant (viral-vectored tobacco) in 1991. After going public at \$17/share in mid-2000, the company’s share price quickly plummeted, ranging from \$0.25-\$2.50 in 2004-2005. LSBC had an operating loss of over \$17 million in 2004.³² The company went bankrupt, was de-listed from the Nasdaq stock exchange, and terminated all of its roughly 70 employees in late December 2005, a development heralded by the *New York Times* as a “setback” for the fledgling pharma crop sector.³³

Ventria Bioscience’s planned move from California to Missouri has collapsed. Ventria, which has no products or revenues, was originally offered a \$30 million subsidy package (with equal contributions to come from federal, state and local sources) to set up shop at Northwest Missouri State University. The company received an additional \$5 million in cash from anonymous investors to cover operating expenses. After failing to raise the federal and local portions of the subsidy package, the dealmakers asked the state to increase its contribution from \$10 to \$23 million.³⁴ MO state legislators balked, leading to a scaled-back version of the project that also failed to gain approval.³⁵

AG GROUPS DIVIDED ON PMPs

While some agribusiness groups like the National Corn Growers Association support PMPs, farmer organizations like the American Corn Growers Association and National Family Farm Coalition are firmly opposed due to concern over

liability to farmers from contamination.³⁶ The Rocky Mountain Farmers Union (RMFU), Western Colorado Congress and 40 other rural & environmental groups have called for a moratorium on outdoor PMP experimentation,³⁷ and were instrumental in stopping a proposed 2003 trial of pharma corn by Meristem Therapeutics. Farmer-led opposition in California and Missouri stopped proposed field trials of pharmaceutical rice by Ventria Bioscience in both states in 2004 and 2005, respectively.³⁸ The opposition in Missouri included two major rice producer trade groups, USA Rice Federation and US Rice Producers Association. The flax industry is fighting attempts by a startup called by biotech start-up Agragen to develop flax genetically engineered to produce a human blood protein due to contamination concerns.³⁹

SCIENTIFIC AND PUBLIC INTEREST GROUPS OPPOSED TO PMPs

Two committees of the National Academy of Sciences have warned of the potential for contamination of food crops with PMP traits, and associated human health risks.⁴⁰ The editors of *Nature Biotechnology*, the industry’s leading journal, recently issued a scathing critique of PMP production in food crops, comparing it to a drug company “packaging its pills in candy wrappers or flour bags or storing its compounds or production batches untended outside the perimeter fence.”⁴¹ A growing list of environmental, consumer protection and public interest science organizations are also opposed to open-air PMP production, especially in food crops. These include Friends of the Earth, Consumers Union, U.S. Public Interest Research Group and Physicians for Social Responsibility of Oregon, among others.

ALTERNATE PRODUCTION PLATFORMS

In 2003, the Scripps Institute announced promising results from engineering algae to produce a range of biopharmaceuticals.⁴² Applied Phytologics (now Ventria Bioscience) has produced an experimental biopharmaceutical to treat cystic fibrosis in a contained fermentation system based on rice cell culture. Another promising experimental technique is rhizosecretion (engineering plants to secrete biopharmaceuticals from their roots) conducted hydroponically.⁴³

THE BIOTECH CASINO

As detailed above, at least three states – Iowa, Virginia and Missouri – have granted or offered generous subsidies to pharma crop

companies in hopes of generating jobs and revenue in their depressed rural economies. Missouri's deal with Ventria has collapsed, while Iowa and Virginia have received no benefit from their investments in ProdiGene and CropTech, respectively.

The truth is that biotechnology has proven to be extremely risky as an economic development tool. "This notion that you lure biotech to your community to save its economy is laughable," says Joseph Cortright, an economist who co-wrote a report on the subject for the respected Brookings Institution. "This is a bad-idea virus that has swept through governors, mayors and economic development officials."⁴⁴ According to Cortright, biotech has become firmly rooted in just three regions – San Francisco, San Diego and Boston – by virtue of their strong venture capital communities, stellar academic institutions and highly-educated workforces (six other major metropolitan areas have established, but less developed biotech industries). Cities and states without these prerequisites have failed, and will likely continue to fail, despite investing millions of dollars in biotech start-ups. Even in the successful biotech centers, jobs and revenues are modest compared to other industries.

Cortright is not alone. In 2004, the *Wall Street Journal* reported that publicly-traded U.S. biotechnology companies lost investors an astounding \$41 billion from 1990-2003.⁴⁵ In 2003 alone, 314 companies racked up losses of \$3.2 billion, and only 12 of the 50 largest in this group posted a profit. 2004 proved even worse, with losses totaling \$6.4 billion.⁴⁶ Comparing biotech firms to 1990's-era "dot.coms," the *Wall Street Journal* noted that: "Biotechnology companies are essentially research and fund-raising machines devoted to selling their scientific and medical "story" to investors and spending the resulting cash on laboratory studies and clinical testing. Some companies survive as long as two decades on investors' largesse without developing a revenue-producing drug. ... the vast majority of biotechs have neither profits nor meaningful revenue and no guarantee they'll ever have either."

Investing in biotech firms, then, is a huge gamble. To quote Cortright: "It's essentially like a casino. There are lots of bets you can lay down, and the potential can be very valuable, but for the most part, the odds that any one will pan out are extremely long."⁴⁷

As bleak as this picture looks, one must keep in mind that the subject is publicly-traded biotech firms, while pharma crop companies are mainly privately-held and funded by venture

capitalists. This suggests that they have not considered sufficiently attractive prospects for initial public offerings. Therefore, PMP companies appear to be even more speculative as investments than publicly-traded biotech firms.

MYTH OF THE BIOTECH REVOLUTION

As suggested above, the experimental pharma crop enterprise must be viewed in the broader context of biotechnology. And since the hoped-for product is a drug, medical rather than agricultural biotechnology is the more appropriate context. Many decision-makers have been influenced by the popular conception of a "biotech revolution" that is supposedly transforming health care and generating substantial employment and revenue for localities lucky enough to lure biotech firms to settle in their regions. In a recent paper,⁴⁸ British social scientists dispute this notion of a biotech revolution, attributing it to several factors. First, there really was an initial spurt of biotech drug approvals as the industry picked the "low-hanging fruit," or technically easy-to-develop drugs, in the 1980s and 1990s; things have slowed down considerably as scientists tackle more difficult medical problems. Even more importantly, they say, biotechnology has been hyped out of all proportion to its true prospects by biotech firms, venture capitalists, financial analysts and others with a vested interest in securing funds for their high-risk development efforts. This hype creates "unrealistic expectations" among policy-makers, leading to "poor investment decisions, misplaced hope and distorted priorities..."

While acknowledging the potential for slow, long-term growth, the UK researchers warn that "the promise of a biotechnology revolution provides government policy-makers with simple, but ... probably ineffective ways of promoting regional development..."

A look at the current stagnation in drug development efforts supports this interpretation. In 2004, our own Food and Drug Administration released a white paper⁴⁹ discussing ways to address a crisis in therapeutics: a significant decline in the number of new drugs in the development pipeline, a rising failure rate as fewer drugs make it through the drug testing process, and skyrocketing drug development costs and prices. The FDA concludes that there is a severe bottleneck in translating basic biomedical research into safe and effective drugs.

Finally, it is worth noting that the 130 plus brand name biotech drugs on the market today have much less therapeutic range and value than the

number suggests. As to range, the 10 top-selling biotech drugs account for half of all sales revenue for this group of 130 plus.⁵⁰ And even among this select group of 10 “blockbusters,” there is considerable overlap. For instance, numbers 1, 2 and 4 on the list are competing versions of the same basic biopharmaceutical, erythropoietin, used to stimulate red blood cell production in patients with anemia caused by kidney failure. As regards benefit, one study has concluded that only 16 biotech pharmaceuticals evaluated between 1986 and 2004 offer better than “minimal improvements” over pre-existing treatments.⁵¹ Finally, the exorbitant price of biotech drugs is creating huge strains on the U.S. health care system.

Thus, even established and successful methods of producing biotech pharmaceuticals are encountering serious obstacles. Technical difficulties are shrinking the pipeline, medical benefit is modest, and high costs are straining the system. The situation can only be more daunting for the fledgling pharma crop sector, which has yet to produce even one FDA-approved drug, despite field trials dating back to 1991.

Where commercial products and revenue are lacking, there is no shortage of hype and dreams. But whether it is ProdiGene’s former CEO predicting millions of acres of pharma corn by 2010,⁵² or Ventrya and its backers promising to turn Maryville, Mo. into biotech’s “Silicon Valley” and make Missouri rice farmers rich, it does not serve the public interest – and indeed, it is morally

reprehensible – to make exaggerated claims and raise false hopes concerning this unproven technique.

CONCLUSION

While far from constituting a revolution, biotechnology has produced some useful, if expensive, products. The \$32 billion biopharmaceutical industry is based on extraction from human and animal tissues as well as proven fermentation systems employing various types of genetically engineered cell cultures. While fermentation systems involve large capital start-up costs, they offer three crucial advantages over the experimental GE plant platform. They work, while GE plants have not. The drugs are *contained*, with virtually no possibility of contaminating the food supply, while 100% containment is impossible with GE plants. And precise *control* over production conditions facilitates a high level of consistency in drug quality and yield, which is not possible with plants grown out-of-doors exposed to a broad range of environmental conditions. Thus, further refinements to traditional fermentation techniques (e.g. Novartis Pharma’s path) or development of alternate techniques like plant cell culture and rhizosecretion that offer the advantages of containment and control appear to be more promising than the GE plant platform in the future development of the biopharmaceutical industry.

¹ Rahul Jasuja, “Protein Drugs: Manufacturing Technologies,” Business Communications, July 2000.

² Walsh, G. “Biopharmaceutical Benchmarks 2003,” Nature Biotechnology, August 2003.

³ “Recombinant Therapeutic Proteins: Delivering a \$53 Billion Mature Market by 2010,” Datamonitor, May 3, 2004, <http://www.marketresearch.com/map/prod/1002431.html>. It is interesting to note that in 2002 Datamonitor forecasted that the market would be \$59 billion by 2010, over 10% higher than the 2004 prediction of \$53 billion. This is a sign of slowing growth (i.e. the “mature market” alluded to above).

⁴ Freese, Bill. “Manufacturing Drugs and Chemicals in Crops: Biopharming Poses New Threats to Consumers, Farmers, Food Companies and the Environment,” July 2002, Friends of the Earth, Section 7.1. www.foe.org/biopharm/

⁵ Based on USDA listings, which by convention are based on date the permit application was received rather than the actual planting date. See USDA GE crop field trial database at www.nbiap.vt.edu/cfdocs/fieldtests1.cfm. Search on “phenotypes” antibody, antibiotic, industrial enzyme(s), pharmaceutical protein, value-added protein and value-added protein for human consumption for the pertinent year. In 2004, USDA launched a new website specifically for high-risk field trials of pharmaceutical and related compounds (http://www.aphis.usda.gov/brs/ph_permits.html). The listings on this latter website are not consistent with the entries in the database cited above. This website has additional listings which I have included in my totals for 2004-2005. The 8 permits for 2004 are: 04-009-01, 04-040-01, 04-044-01, 04-044-02, 04-104-01, 04-114-01, 04-131-01, 04-355-01; the 11 permits for 2005 are: 05-025-01, 05-025-02, 05-025-03, 05-053-01, 05-061-01, 05-069-01, 05-073-01, 05-087-01, 05-090-01, 05-117-01, 05-117-02.

⁶ Freese, op. cit., Sections 4.1 to 4.4. On immune reactions, see also <http://www.foe.org/biopharm/commentsguidance.pdf>, pp. 23-24.

⁷ According to Hugh Mason, a leading researcher in the field of edible vaccine. See “Plant-Derived Biologics Meeting,” held on April 5 & 6 in Ames, Iowa. April 6th transcript, pp. 88-89. <http://www.fda.gov/cber/minutes/plnt2040600.pdf>.

⁸ According to Dr. Allison Snow, professor of evolution, ecology and organismal biology at Ohio State University in Columbus, in comments at the “The Future of Pharming: Can It Be Done Safely?” a science policy forum sponsored by Center for Science in the Public Interest, National Press Club, Washington, DC, Dec. 17, 2002.

⁹ Maier, Dirk. “Concerns over Pharmaceutical Traits in Grains and Oilseeds,” Fact Sheet #47, Grain Quality Task Force, Purdue University, July 2, 2002. <http://www.ces.purdue.edu/extmedia/GQ/GQ-47.pdf>.

- ¹⁰ "No Use of Food or Feed Crops for Plant-Made Pharmaceutical Production Without A '100% Guarantee' Against Any Contamination , Says NFPA," Press Release, National Food Processors Association, Feb. 6, 2003. http://www.nfpa-food.org/News_Release/020603NewsRelease.htm.
- ¹¹ Guy, Sandra. "Kraft exec wants tougher rules on planting crops for drugs," *Chicago Sun-Times*, April 4, 2003.
- ¹² Cancelada, G. & Lambrecht, B. "Brewery may shun rice from Missouri," *St. Louis Post-Dispatch*, 4/11/05
- ¹³ Toner, Mike. "Alarms sound over 'biopharming'; Tainted crops cast doubt on gene altering," *The Atlanta Journal and Constitution*, Nov. 17, 2002.
- ¹⁴ "Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds," *Federal Register*, Vol. 68, No. 46, 3/10/03, pp. 11337-40.
- ¹⁵ "What is the compliance history with APHIS' biotechnology regulations?" USDA Animal and Plant Health Inspection Service, posted October 2003. <http://www.aphis.usda.gov/brs/compliance9.html>.
- ¹⁶ "Audit Report: Animal and Plant Health Inspection Service Controls Over Issuance of Genetically Engineered Organism Release Permits," Office of Inspector General, Southwest Region, USDA, Audit 50601-8-Te, December 2005, <http://www.usda.gov/oig/webdocs/50601-08-TE.pdf>
- ¹⁷ Gillis, J. "Firm Fined For Altered Corn in Soybeans: \$250,000 Levy Is First In Genetic Food Case," *The Washington Post*, Dec. 7, 2002.
- ¹⁸ "Statement on the Use of Food and Feed Crops for the Production of Plant-made Pharmaceuticals and Industrial Products," North American Millers' Association, October 2002. http://www.namamillers.org/cs_biopharm.html.
- ¹⁹ As quoted in Philipkoski, K. "Food biotech is risky business," *Wired News*, 12/1/03. <http://www.wired.com/news/medtech/0,1286,61096,00.html>.
- ²⁰ According to Thomas Greany, senior vice president of the risk-management firm Marsh, coverage available to biotech companies has fallen from \$1 billion to \$700 million over the past three years. See "Food biotech is risky business" above.
- ²¹ Carr, Paul. "Corn growers faced with decision about proposed StarLink settlement," *University of Minnesota Extension Service*, March 18, 2003.
- ²² "Plants: A competitive alternative to produce biopharmaceuticals?" a presentation by Dr. Hans P. Kocher of Novartis Pharma of Basel, Switzerland, at the "Plant-Manufactured Pharmaceuticals" Symposium sponsored by the San Diego Center for Molecular Agriculture, October 17, 2003.
- ²³ Monsanto CEO Hugh Grant, as quoted in: Pollack, Andrew. "Monsanto Overhauling Businesses," *The New York Times*, 10/16/03.
- ²⁴ Graff, G. "Crop Biomanufacturing: Part 1: The Economic Opportunity," *Bio Economic Research Associates*, Jan. 2004
- ²⁵ Presentation by Jean Roberts of Dow Agrosiences at the "Plant-Manufactured Pharmaceuticals" Symposium sponsored by the San Diego Center for Molecular Agriculture, October 16, 2003.
- ²⁶ Kauffman, C. "Investments drain state money," *Des Moines Register*, 4/27/03
- ²⁷ Gillis, J. "U.S. Will Subsidize Cleanup of Altered Corn," *Washington Post*, 3/26/03; Johnson, Dale. "Stine Seed purchases biotech company ProdiGene," *The Spokesman, Iowa Farm Bureau*, Aug. 25, 2003. <http://www.ifbf.org/publication/spokesman/story.asp?number=21545&type=News>
- ²⁸ Crabtree, P. "Epicyte Pharmaceutical joins failing-biotech row," *San Diego Union Tribune*, 5/7/04.
- ²⁹ "Biolex Acquires Epicyte Pharmaceutical," *Biolex press release*, 5/6/04. www.biolex.com/pdfs/Biolex%20Acquires%20Epicyte.pdf.
- ³⁰ Freese, B., op. cit., p. 64.
- ³¹ Ranii, David. "Biotech company files for bankruptcy: CropTech files for bankruptcy," *Raleigh News and Observer*, April 25, 2003. <http://www.nasvf.org/web/allpress.nsf/pages/6771>.
- ³² Information gleaned from Yahoo Finance, 11/30/05. Search on "Large Scale Biology Corp" or "LSBC."
- ³³ Pollack, A. "Biotech company closes after running out of cash," *New York Times*, 12-24-05
- ³⁴ "Biopharming company's plans to move to Missouri stalled," *AP* 11/16/05, <http://www.centredaily.com/mld/centredaily/business/13183200.htm>; "Regents OK biologics center financing," *Press Release, Northwest Missouri State University*, 9/21/05, <http://www.nwmissouri.edu/UniversityRelations/news/NEWSRELEASES/050921RegentsOK.htm>
- ³⁵ "Ventria cancels move to Northwest Missouri," *Colombia Tribune*, December 31, 2005, <http://www.columbiatribune.com/2005/Dec/20051231News011.asp>
- ³⁶ "Food Processors and Grocery Manufacturers Confirm Corn Grower Concerns About Use Of Genetically Modified Crops To Make Drugs and Chemicals," *American Corn Growers Association press release*, Nov. 12, 2002. <http://www.acga.org/news/2002/111202.htm>.
- ³⁷ "Governor's office fails to respond to biopharm moratorium request," *Rocky Mountain Farmers' Union press release*: May 12, 2003. <http://www.rmfu.org/News/Releases/ShowNews.cfm?ID=191>.
- ³⁸ Silber, J. "Permit for biotech rice is denied," *Contra Costa Times*, 4/9/04; Bennett, B. "Ventria BioScience finds Missouri producers unwelcoming," *Delta Farm Press*, 5/26/05, <http://deltafarmpress.com/news/050525-ventria-rice/>.
- ³⁹ Hoffert, E. "VIEWPOINT: Agragen sows a crop of false assertions," *Grand Forks Herald*, 6/26/05, <http://www.grandforks.com/mld/grandforks/news/editorial/11987962.htm>
- ⁴⁰ "Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation," *National Academy Press* 2002, p. 68. <http://books.nap.edu/catalog/10258.html>. "Biological Confinement of Genetically Engineered Organisms," *National Academy Press* 2004. <http://www.nap.edu/catalog/10880.html>.
- ⁴¹ "Drugs in crops – the unpalatable truth," editorial, *Nature Biotechnology* 22(2), Feb. 2004, p. 133.
- ⁴² "Growing Human Antibodies in Algae is an Inexpensive and Fast Route to Large-Scale Production, Say Scientists at The Scripps Research Institute," *Press Release, The Scripps Research Institute*, January 15, 2003.
- ⁴³ For an overview of alternative production systems, see Freese, B. op. cit., Appendix 5.
- ⁴⁴ Elias, P. "States, cities court biotech, but is it worth it?" *Associated Press*, June 9, 2004; Cortright, J. & Mayer, H. (2002). *Signs of Life: The Growth of Biotechnology Centers in the U.S.*, The Brookings Institution. <http://www.brookings.edu/metro/publications/biotech.htm>.
- ⁴⁵ Hamilton, D. "Biotech's Dismal Bottom Line: More Than \$40 Billion in Losses," *Wall Street Journal*, May 20, 2004
- ⁴⁶ Elias, P. "Biotechnology Loses Billions A Year," *Associated Press*, 6/1/05.
- ⁴⁷ *Ibid.*
- ⁴⁸ Nightingale, P & Martin, P. "The myth of the biotech revolution," *TRENDS in Biotechnology*, 22(11), Nov. 2004, pp 564-569.
- ⁴⁹ Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products," *U.S. Food and Drug Administration*, March 2004, <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>
- ⁵⁰ Lawrence, S. "Biotech drug market steadily expands," *Nature Biotechnology* 23(12), Dec. 2005, p. 1466.
- ⁵¹ Nightingale, P & Martin, P., op. cit.
- ⁵² Former CEO Anthony Laos, as quoted in: Zitner, A. "Fields of Gene Factories," *Los Angeles Times*, June 4, 2001