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## Fields of Dilemma: Recent Events in Biotechnology and Crop Production

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***Pharming the future?*** Recent discoveries in the biological sciences are providing new ways to beneficially manipulate biological systems ranging from individual cells to entire ecosystems. The engineering of biological systems can increase the quality, quantity, and production efficiency of a myriad of food and non-food products.

In many Midwestern states, this has been translated into what has been described as the new biotechnological vision of agriculture. This new technological gestalt is envisioned as a source of renewed hope for the future of Midwestern farming. This technological solution to move from commodity-only production systems is quite attractive to producers for a number of reasons, but two are paramount: First, it allows farm families to continue to preserve a cultural link to their land and local communities. Second, the technology promises to provide a new high-value “economic engine” for rural communities, promoting the location of “biorefinery” and similar “industries-of-the-future” and encouraging the movement of high-wage skilled technical employment to states that have lost, or have failed to develop, those types of industries for several decades. Additionally, the most sophisticated of established U.S. producers, particularly those involved in hybrid seed or similar specialty crop production, are poised to adapt to new identity-preserved production systems with minimal changes to their current operations.

***How did we get here?*** Many of the progenitors of the agricultural biotechnology movement, Monsanto Co., Du Pont/Pioneer, Bayer/Aventis and Dow have decades of investment in proprietary technologies and germ-plasm banks. Thirty years ago, most of these companies, or

their progenitors, recognized the potential of biotechnology to expand their product lines into hitherto unreachable food and non-food areas. However, by industrial necessity and with respect to the technology available at the time, initial applications for genes inserted from different organisms into crops focused on developing insect resistance, herbicide-resistance, or to improve specific nutritional or functional properties. Consequently, government regulations and industry guidelines evolved to enable biotechnology to go safely forward within a framework of general scientific self-oversight.

However, within the last 20 years, molecular biology and genetics have intermingled, creating the emerging field of “Transgenics.” Transgenics is the transfer of genetic material from one species to another, within and between animal and plant systems, and all of the biological tools necessary to do this. As the technological tools for gene mapping, sequencing, and recombination became increasingly “cook-book” more newcomer biotechnology companies, spurred on by the headlong venture-capitalist technology investment and Initial Public Offering mania of the 1990s, entered the international business landscape. Many of these companies were or are joint ventures, spin-offs, and wholly owned subsidiaries of major agribusiness, chemical, pharmaceutical or consumer products companies.

These companies, in turn, have developed adventitious strategic relationships with large agricultural biotechnology and pharmaceutical leaders such as Eli Lilly, Du Pont/Pioneer, Bayer/Aventis, Pfizer Inc., etc., to access development capital and brand identification; as well as to access the established testing, marketing, and global distribution systems of these companies.

This “Living Factory” concept is attractive to the industries involved, for several reasons. Crop plants are an inexpensive way to produce a wide range of specialty proteins. Also, by incorporating regulatory genes that control how a target protein is produced, biotechnologists can “dial-in” the degree of “expression” or production of that protein within a carrier, probably cornstarch or zein (the corn protein fraction). For illustrative purposes, let us say that the protein is a non-fattening sweetener. This would mean that a client, perhaps a food company, could order cornstarch “pre-set” to a given sweetness level. They would have no need to incorporate corn syrup, white sugar or any of the equipment required for storage, handling or incorporating these ingredients.

Plant-based production has revolutionary implications for many industries. This is particularly true for pharmaceutical production. “Pharming” is the term being applied to Plant Manufactured Pharmaceutical (PMP) crop technology. If a protein, for example, a human antibiotic, is derived from animal sources, the expense, severe production limitations, and ethical dilemmas of that production system could become mute points. Instead of being able to produce a few hundred very costly liters of a rare vaccine, a company could manufacture quantities limited only by the acres available for production. Additionally, the product-isolation techniques could be far less quality control intensive, and far less expensive. Even administering the final product may be simplified. Instead of injecting a child with a vaccine, one could just give him or her, for example, a confectionary product for oral consumption that contains the protein.

So why produce these proteins in crop plants like corn (maize)? Plant breeders, agronomists, and growers know corn. Corn, and soybeans are established well-developed production systems that have been utilized and modified by humans for thousands of years. Additionally, these crops have no immediately out-crossable wild relatives, so there is no danger of the genetic contamination of native plants. Other crop-specific mechanisms, like male sterility or temporal

and spatial isolation can be exploited to control out-crossing between different varieties. Additionally, at this writing, transgenic animals are being used to produce therapeutic quantities of human proteins in animal milk. However, due to animal-borne diseases such as BSE (bovine spongiform encephalopathy, aka. nvCJD or “Mad Cow Disease”), there has been increased concern about the safety of transgenic proteins from animal sources.

Success in deciphering the human genome, advances in medical research, and the understanding of complex protein interactions, has led to the rapid discovery and development of a myriad of new therapeutic compounds and revolutionary ways for fighting and preventing disease. As a result, approval rates for new drugs are expected to reach record highs in the next few years. Over half of the products on the market today were approved within the last five years, and an estimated 50 to 60 product approvals will be granted over the next six to seven years. Of particular importance is the recombinant therapeutic protein market. Today, it is over \$17 billion in annual sales, and that figure could double over the next five years. In addition to this, the predicted market for industrial proteins is expected to be \$2 billion by 2004.

***So what is in the PMP pipeline?*** At this writing, several truly revolutionary products developed for pharma-corn (PMP) production systems are in the final stages of product-recovery, agronomic testing, or pre-commercialization trials.

*These include:*

- Replacing limited, high-cost animal production systems for the protein Aprotinin, indispensable for controlling blood clotting during open-heart and other surgeries;
- a more affordable and readily available hepatitis-B vaccine;
- a novel topical treatment for herpes viruses;
- a revolutionary cancer-cell growth inhibitor;
- human insulin from a plant source;
- a more affordable and readily available cervical cancer vaccine;
- a digestive enzyme aid to drastically improve the day-to-day lives of cystic fibrosis patients;
- an affordable and readily available, edible AIDS vaccine.

And these are simply the vanguard products from what could become an established and broad-based economic and production platform. In time, transgenic technology could produce any protein needed for human health, veterinary or industrial markets. Almost any protein, at least theoretically, could be produced on a large scale in crop plants.

***A need for protein manufacturing capacity.*** Within commercial transgenic crop biotechnology, industry leaders like ProdiGene, and the French biotechnology company Meristem Therapeutics have been at the forefront of the race to develop systems for large-scale production and product-recovery of specialty proteins within corn. These companies have recognized the following fact about the agricultural biotech revolution:

U.S. and European companies are rapidly exhausting the available manufacturing capacity (primarily fermentation) for recombinant proteins. Consequently, industry is being forced to recognize that the number of protein-based products being developed could exponentially exceed conventional protein manufacturing capacity. To meet the estimated demand for production

capacity, a bare minimum of \$5 to \$6-billion of capital will be required to satisfy near term needs. However, even if traditional fermentation manufacturers were to triple or quadruple their facilities, at a considerable cost in time and capital, they would not be able to meet anticipated demand. Due to the scarcity of manufacturing resources, at current capacity levels, a minimum of two-thirds of pipeline products will never make it to market or will experience significant delays.

For this reason, both Prodigene and Meristem are pioneering the use of transgenic plants to produce recombinant proteins for the pharmaceutical, animal health and industrial protein and enzyme markets. Using transgenic plants as pharmaceutical factories, these companies are employing proven technologies to provide high purity, non-animal-source proteins, potentially at very large production scales and at significantly lower costs than those of conventional fermentation and other emerging technologies. Their protein products can be provided in purified form or in an edible form for oral administration. Both types of products can be manufactured, purified, shipped and delivered at lower cost than those from other available production methods. Widespread crop-plant-based protein manufacturing has the potential to make many current high-cost biotechnology production systems obsolete in a very short time.

Using proprietary maize platform technologies, ProdiGene, Meristem, and similar ventures can supply high volumes of proteins, quickly capitalizing on emergency production needs, manufacturing capacity shortages, or similar market opportunities. The ProdiGene corporate milestone timeline projects a clear picture of the rapidity and scope of this production technology:

#### *ProdiGene's Historical Milestones*

- 12 Aug 2002: NIH oral vaccine trials.
- 16 July 2002: Aprotinin scale-up.
- 05 June 2002: Gelatine from maize (non-animal source).
- 13 Feb 2002: World's first large-scale recombinant protein production from plants announced.
- 13 May 2001: Patent honored by MIT.
- 13 May 2001: Enzyme production with Eli Lilly and Company.
- 09 May 2001: Avant agreement to manufacture pharmaceutical protein.
- 09 May 2001: Therapeutic Protein agreement to manufacture pharmaceutical protein.
- 28 Nov 2000: NIH edible AIDS vaccine grant.
- 31 Oct 2000: Oral vaccine patent granted.
- 25 June 2000: Protease manufacturing patent granted.
- 05 April 2000: Industrial enzyme patent granted.
- 15 Feb 2000: Edible vaccine demonstrated.
- 20 July 1999: Edible vaccine for viral diseases patent granted.
- 18 Mar 1999: Second alliance with Genencor International Inc.
- 15 June 1998: Alliance with Epicyte Pharmaceutical, Inc.
- 22 April 1998: Alliance with Nektar Therapeutics.
- 23 Oct 1997: First alliance with Genencor International Inc.
- 10 Nov 1996: "Spin-off" from DuPont/Pioneer (Pioneer Hi-Bred, Int., Inc.)

Sources: Washington Post and ProdiGene News Wire.

***Big mistakes, big problems, big questions.*** Recent events have called into question several concerns regarding whether or not bio-farming production systems can exist within the current system of government regulation and self-regulatory industry guidelines.

During the 2001 growing season, ProdiGene had nursery plots in Nebraska and Iowa. Both sites were small fields, about an acre or so, where transgenic test grow-outs, known as “events,” were planted. These were not full-scale “production for product” trials. The Nebraska test plot was a research nursery plot that contained four to five different events. At the end of the growing season, all material in the fields was either harvested or removed and destroyed. The following year, according to the isolation plan, soybeans were planted on these acres, and the area regularly checked for volunteer corn plants from the previous season. These were then “rogued” (individually removed by hand).

In the fall of 2002, a farmer, harvesting the soybean crop stated that he observed two to three volunteer corn plants, 10 to 15-inches tall. Apparently, these plants had been concealed by the soybean canopy while it was leafy and green. It was estimated by the USDA and ProdiGene that this material totaled 25 grams of foreign-corn-matter contaminant. The farmer did not stop to remove these two or three plants, instead, he ran them through his combine with the soybeans as he continued to harvest. The 25 grams of corn leaf and stalk contaminant (no seed or germplasm material) was mixed into 500 bushels of soybeans taken from the field. This was a major error. However, the worst was yet to come. The contaminated beans were subsequently transported to the local elevator where they were mixed into 500,000 bushels of soybeans already in storage.

It is important to note once again that the contaminated material was corn stalk and leaf residue. The plants were immature volunteers. There was no seed present. The transgenic germplasm usually is expressed in the seed for most PMP crops. Therefore, sexual out-crossing and escape of any transgenic material into any other corn crop was, most likely, physically impossible.

A thorough examination of the recovered contaminant corn from the elevator by the USDA and ProdiGene failed to detect any trace of “foreign protein.” Analysis suggested that the contaminant corn-plant material could have originated from the benign non-transgenic variety used in the plot’s border isolation rows, or perhaps from common grain transported from a more distant and equally benign source. However, due to the zero-tolerance agreement, this residue contamination resulted in fines and a December, 2002, financial liability settlement with the USDA. ProdiGene received a \$250,000 fine, was required to post a \$1-million bond (USDA Plant Protection Act), and was required to “take responsibility” (pledges to reimburse the USDA) for the \$3-million cost of purchase, removal and destruction of the 500,000 bushels of “contaminated” soybeans from the elevator. In February 2003, the beans were incinerated at a local power generation facility.

Although no type of transgenic contamination occurred on any level, and the only corn contamination was from the leaf and stalk material of two or three non-sexually expressive plants, the environmental- and social-activist organization Greenpeace was able to use the incident to develop an international media event that included unfurling a huge banner from the grain elevator portraying a syringe injecting a corn cob with the statement, “This is your food on drugs.” Little to no information on the actual level of contamination has subsequently appeared

in the national or international press. The fines, concerns by industry groups, and the outrage of environmental groups, were well covered.

So what did ProdiGene do wrong? First of all, the company should have been cognizant and vigilant of the potential for a problem. As early as 2001 the writing was on the wall that regulatory agencies and the public would not tolerate biotechnological screw-ups. This was the legacy of the Bayer/Aventis Starlink corn debacle.

Aventis CropScience StarLink was a transgenic variety of altered corn for the animal feed market. It contained a modified gene to increase the corn plant's insect resistance through the production of *Bt* (*Bacillus thuringiensis*) protein toxin. *Bacillus thuringiensis* a common soil bacterium, has been used for decades by organic gardeners and nurserymen for insect control. However, this Bt gene/protein isolate, Cry9C, unlike other Bt proteins, was classed as a suspected human allergen based on its resistance to heat degradation and digestion (a characteristic of many allergens), although no actual evidence of human allergenicity exists for any Bt toxin. Additionally, Cry9C had not undergone the U.S. regulatory process to have its use approved for human food. For this reason, it was not approved for export to the European Union.

Aventis, through representatives and in writing, directed growers to properly isolate, plant, harvest and utilize the grain. Yet, this did not happen. A lack of proper lot segregation, failure to follow field segregation procedures, and poor custodial equipment and storage maintenance resulted in widespread low-level contamination of corn stores destined for human food products. The resulting regulatory and public panic forced elevators and shippers to aggressively deal with the problem. Costly testing, prophylactic isolation and non-food disposal of any suspected corn created considerable monetary hardship for producers, elevators, handlers, shippers and some end-users. Although, government hearings proved that there was a greater "perceived" incident than any actual threat to human health (the protein would have been present in virtually insignificant amounts in any of the refined-corn product streams that it could have entered), the incident promoted fear and mistrust, from grower to consumer, throughout the production chain. Testing for StarLink indicated or suggested its presence, at least in trace amounts, in 50 percent of U.S. corn supplies, as well as some international grain shipments. This resulted in media and environmental group outcries in Europe and Japan. As recently as January 2003, Starlink was recovered in Japan from a 19,000-ton corn shipment meant for human consumption.

It should be noted that Starlink corn, approved for animal consumption, made its way, in part due to curious regulatory policies, into widely marketed and consumed corn taco shells. After the discovery of Starlink contamination, twenty-four individuals came forward with claims of severe allergic reactions to corn products suspected of containing Starlink. Seventeen of these individuals consented to providing USDA and CDC investigators with blood samples. The June 13, 2001, CDC-released report concluded that some of the claimants did appear to have had severe allergic reactions to some agent, but that they were not allergic to Cry9C/Starlink. Furthermore, the U.S. Centers for Disease Control found no evidence of any allergic reactions related to the trace-level contamination. However, the EPA scientific advisory panel on Starlink determined that although CDC/FDA findings demonstrated that the individuals who came forward were not allergic to Cry9C/Starlink, this did not, in itself, rule out the possibility that human allergenicity could exist. For this reason, in July 13, 2001, the EPA ruled against a petition by Aventis (hoping to allow trace amounts of Starlink in the food supply), and reasserted the standing EPA zero-tolerance policy for Cry9C protein presence.

ProdiGene should have gleaned two very useful observations from the Starlink incident. Aventis trusted the growers to read and follow the written guidelines for producing the specialty crop. Many growers did not do so. Aventis trusted the growers to ensure proper field sanitation practices. Again, many growers did not do so.

In the ProdiGene incident in Nebraska, and to a far lesser extent in a less publicized Iowa incident, local sub-contractor consultants of an allied seed company (not the growers, not the parent company) were responsible for overseeing agronomic operations. Additionally, no clear guidelines were defined on the extent to which federal rules would continue to remain in effect “post-harvest.” It is now recognized that the Nebraska plot, plowed and replanted to beans, should have been left fallow for a season. Diligent monitoring by the agronomic consultant and the individual producers working the land could have circumvented a costly international incident. All that was really needed was for the consultant to check the field after the bean crop’s leaf canopy dried, and remove a couple of plants, or for the combine operator to get down from his machine, pull the corn plants and take them back into the cab with him (subsequently, these corn plants could have been completely tested for transgenic protein or varietal markers to ascertain their true origin).

Continued monitoring, and an informed grower could have prevented the incident. However, at the time the incident occurred, neither the consultant, nor the grower felt that they were in any way responsible for any material left in the field. ProdiGene in far-off College Station, Texas, was the permit holder and was the legally responsible party.

The damage was done. What can best be described as a ProdiGene/Starlink backlash resulted in increased scrutiny of the entire agricultural-biotechnology industry. In November and December, 2002, increased scrutiny by the USDA and EPA resulted in Dow AgroSciences being fined \$8,800 by the EPA for failing to plant a wind-block tree-line buffer zone around a test plot, and DuPont/Pioneer being fined \$9,900 by the EPA for a similar isolation issue for a less than 1-acre research plot at a dedicated non-production research facility on Kauai, Hawaii.

Far-reaching policy implications soon followed. The ProdiGene news did not help the U.S. position in the World Trade Organization (WTO) dispute with the European Union over issues regarding mandatory warning labels. The proposed legislation would require a product to wear a warning label if genetically modified organisms (GMOs) are used at any point in its ingredient stream or production process, even if those GMOs or their products are undetectable in the final product. Additionally, the incident occurred while the U.S. was acting through the WTO to end the current moratorium on new GMO approvals for EU importation. It is projected that these policies cost U.S. farmers \$300-million/year.

Perhaps more significantly, here in the U.S., the Biotechnology Industry Organization (BIO), pressed by Grocery Manufacturer’s Association (GMA) and National Food Processors Association (NFPA), reached a decision to impose a “self-imposed” moratorium on growing transgenic crops in food grain production regions.

Immediately thereafter, the North American Millers’ Association (NAMA), the representative body for the primary suppliers to the American bakery and prepared-food industries, released the NAMA Resolution. This statement asserted a zero-tolerance policy for pharmaceuticals and

industrial chemicals in the food-grain production stream, yet promoted a “non-zero-tolerance” “Adventitious Presence” (AP) policy to protect millers and end-users.

*Summary: North American Millers’ Association Position Statement.*

- NAMA supports biotechnology and recognizes its potential benefits; however:
- The presence of plant-made pharmaceuticals and industrial chemicals in products meant for food and feed is not allowable at any level.
- Current regulatory standards enforce “zero tolerance,” creating unacceptable risk for U.S. food processors.
- Concern that current (production and segregation) procedures cannot control 100 percent of the genetic material... or prevent deliberate evasion.
- Even the slightest risk of adulteration of food supplies is unacceptable.
- Preventing adulteration is the responsibility of the technology developer and U.S. regulatory agencies.
- NAMA supports physical containment and temporal separation for 100 percent isolation.
- NAMA supports mandatory liability insurance coverage for agricultural biotechnology firms and producers.
- Creation of AP testing protocols before granting permits.
- NAMA demands compliance with, and enforcement of, zero percent contamination policies.
- NAMA supports the establishment of a reasonable AP policy and screening of all new crop-biotechnology products for toxicity and allergenicity. This would permit AP in trace amounts and alleviate many current problems.

The GMA, NFPA, and NAMA positions were troubling, but of immediate concern was the BIO group’s decision to voluntarily suspend transgenic PMP crop testing.

According to the BIO statement: "Science has shown that out-crossing crops [like corn] can be used safely for plant-made pharmaceuticals and industrial purposes, and regulations are in place to safeguard against out-crossing from these crops to crops intended for food and feed purposes." Despite the safety of the technology, "BIO members have chosen to go a step beyond science and regulation to demonstrate good stewardship for this new technology."

At first glance, the industry's decision seems prudent, isolating food production from drug production and taking sensible steps to assure the safe scientific development of a new technology. It also had the potential to derailing a high-value industry for the financially strapped heartland.

With a voluntary suspension of production in the “corn belt,” Iowa in particular, was faced with a serious problem. Studies by the BIO group, echoed by research from Iowa State University, conservatively estimated the potential for specialty value-added PMP “Pharming” of pharmaceutical and similar high-value proteins to be a \$14-billion industry by 2005. This promoted immediate responses from Iowa’s Democratic Governor Tom Vilsac, and senior Republican U.S. Senator Charles Grassley to respectfully confront the BIO group’s decision and request that they revise their policy based on workable, practical production systems and regulatory guidelines.

The official response to the BIO statement on PMP crops was formulated by Dr. Steven Howell, Director, ISU Plant Sciences Institute. In the BIO response document Howell emphasizes the following points:

*Summary: ISU Response to BIO Position Statement.*

- Industry estimates are that PMP production will be a \$12 to \$14-billion industry by 2005.
- Highest priorities: safeguard Iowa's agricultural resource and maintain public confidence.
- Iowa must not be left out of the benefits and promise offered by the PMP industry.
- It has been proven that PMPs can be produced in a safe, well-managed, and environmentally friendly way.
- It has been proven that physical and biological containment systems work, particularly when "stacked."

The official response also noted the venerable Starlink debacle: "We all have been sensitized and educated by the Starlink Incident. Starlink was a wakeup call to warn us that systems were not in place to handle specialty crops not intended for human consumption. We have taken many actions to make sure that a 'Starlink' will not happen again," Howell wrote.

The Iowa response succeeded in prompting the BIO industry organization to, at least publicly, rescind their moratorium on transgenic plantings in Iowa. However, it is doubtful whether or not any transgenic acres will be planted in 2003. Personal communication with individuals from the industry suggest that firms will take a "wait and see" position on field trials for 2003, or until some of the more pressing regulatory (especially adventitious presence standards) and liability issues are defined.

***A practical approach and a shining example.*** The ISU response was, in part based on the research expertise of Iowa State University, and established international agricultural biotechnology leaders like Iowa-headquartered DuPont/Pioneer, and in particular, the crop-production systems developed by Horan Brothers Specialty Crops.

Located in Knierem, IA, Horan Brothers Specialty Crops has been quietly, and flawlessly producing transgenic crops for Meristem Therapeutics Inc., Clermont-Ferrand, France, for two seasons. Bill and Joe Horan, innovative producers, prepared the model for their production and delivery system, put together a business plan and traveled to Clermont-Ferrand where they presented it to Meristem executives and research scientists. This resulted in a cooperative agreement for the Horan brothers to oversee transgenic corn production on their acreage. One of the strengths of the Meristem/Horan arrangement, unlike the ProdiGene arrangement, is that Horan Brothers Specialty Crops is the permit holder, not Meristem Therapeutics. In this model, the Horan brothers are immediately accountable for all aspects of transgenic crop production on their land, up to and including any movement of that material into neighboring crops, and proper shipment of the final product to its owner Meristem.

*Key aspects of an effective system:*

- Grower holds the 2-year federal permit.

- The PMP crop is planted at least 1/4-mile (400-meter) from other production corn (establishing a “set-back” barrier to pollen drift).
- PMP crops are planted at least 21 days after other production crops (establishing temporal pollen isolation).
- The PMPs are male-sterile transgenic lines that cannot produce pollen.
- The PMP male-sterile lines are immediately de-tasseled, and continuously monitored for late tassels or tassels missed during prior detasseling operations.
- Commercial varieties are planted to pollinate the PMP variety then mowed prior to any possibility of contamination by the PMP variety. (This prevents commercial-origin volunteers carrying PMP germplasm, even though the PMP is a male-sterile line, has been detasseled, and has been continually monitored for any tassel development).
- A 100-yard fallow barrier of bare earth or low ground cover is planted around the PMP field to aid in field cleanliness, field clean-up and monitoring.
- Separate PMP-dedicated production equipment and secure storage for crop and equipment is maintained in locked, access logged, and monitored facilities.
- A mass-balance system was designed to monitor grain from field to user. It is used to account for every gram of specialty crop material.
- Any harvest waste is incinerated and the ashes inspected and buried on site.
- All production, shipping, and clean-up operations are logged or labeled, signed, dated, and witnessed by at least two individuals.

The Horan brothers have established a system that can work well in the Midwest, one that uses triple to quadruple redundant procedures to ensure that out-crossing does not occur, and meticulous field care to ensure against rogue plant establishment. Of course, no system is flawless or idiot proof. But this one is a well-designed agronomic system that, thus far, has worked to perfection.

In 2001 the Horan Brothers produced 25-acres of PMP corn, and in 2002, 1-acre; however, production in 2003 is questionable. So far, no acres will be planted at their farm or elsewhere in Iowa. Some PMP firms are in discussion with the Horan’s about managing their trials and grow outs in other non-corn-belt locations. The firms clearly are taking a wait-and-see attitude with respect to Midwestern production, and tending to gravitate toward “non-corn-belt” locations for plantings.

***The Challenges and the Reality.*** In discussions with ProdiGene, the Horan brothers, and researchers at Iowa State University, it is clear that there is firm belief that a practical management approach to PMP production will prevail. But what are the important cornerstones of any practical regulatory and production system?

First, there is a need to establish supply chain “tolerance levels” for exotic proteins, before these crops ever make it into the field. At what levels should purity be established when there are no food-safety issues? Zero-tolerance policies may have political appeal to special-interest groups and the majority of consumers, but they are far from practical, and with respect to many of specialty proteins that may be produced in corn, concern over harm to human health from ingesting them is nonsensical. However, the organic, “pure foods,” and environmental movements will be difficult to sway from their current zero-tolerance positions.

Secondly, the establishment of practical and cost-effective testing protocols could do a great deal to maintain lot purity and aid in spot-checks of stored and shipped non-PMP grain. These systems and protocols are in place for some GM varieties and others are being developed.

If you can eat corn containing a particular protein and it is destroyed in the digestion process leaving no harmful sub-products, is it in any way a health threat? An immediate government ruling on the “open” production of those PMP and industrial proteins that are benign when ingested (most GM-proteins must be recovered, refined, or “activated” to become fully functional), would do a great deal to get many urgently needed new products to consumers. However, this could result in “pure foods” advocates claiming psychological harm from being forced to consume, what is to them, contaminated food. This could result in their pressuring food manufacturers and marketers through negative advertising, boycotts, or legal action.

However, there are other serious issues: Can GM and non-GM technologies co-exist? Can costly or irreversible human error be prevented? Will adventitious presence (AP) standards result in widespread low-level contamination from various sources, and then create a challenge to find “clean” grain if it is so desired by specialty product end-users? Could PMP production drive “clean” non-GM seed producers “off shore” to ensure isolation and germplasm separation? This could result in severe expense for many seed producers, as well as the loss of U.S. jobs and an established value-added agricultural industry.

Perhaps some PMP or industrial proteins may not be suitable for open-crop production systems. In these cases, physical isolation (contained within a greenhouse) or “remote-area production” (geographic segregation) of PMP crops will be an attractive option or outright necessity for some firms, particularly if the proteins are in any way public-relations or human-health “sensitive.” In these situations the high-costs of irrigation or greenhouse production would easily be offset by the high-values of the resulting products. Additionally, the increased segregation could lessen concerns unrelated to out-crossing, e.g., crop vandalism, industrial espionage, or theft.

*Immediate questions and lessons for the PMP industry:*

- Is there any situation where any subcontractors be trusted if they are not the permit holders?
- Does the current regulatory system work? Is it equitable and does it prevent incidents? (Probably not.)
- If the current regulatory system does not work, who should participate in the debate to amend it? How should it be amended?
- Only select growers can be trusted to ensure 100-percent procedural and regulatory compliance, and they must be the permit holders.
- As long as clinical trials will take three to five years, there is no need for large-acreage open grow-outs? (These can be done in contained greenhouse situations.)

A recent Reuters press article reiterated that the high cost and uncertain pay-off from genetically altered crops are major factors behind the increasing concentration of PMP research into a handful of firms. Citing a study of the industry by Bio Economic Research Associates, Cambridge, MA, a consulting firm, four firms account for 57 percent of GM crop research and

development. Agrochemical firms headed its list of 180 firms, universities and government agencies active in agricultural biotechnology.

The case study stressed that development of a GM plant variety can take six to 12 years and cost from \$50 to \$300-million, and still face consumer- and marketplace-acceptance risks. For this reason, the following well capitalized, large firms: Monsanto Co., DuPont/Pioneer, Bayer/Aventis and Dow, were the four leading companies in bio-crop research and development. These firms have strategic alliances and partnership agreements with a dozens of specialized crop-biotechnology firms (including ProdiGene and Meristem Therapeutics Inc.).

The Bio Economic Research Associates report stressed that in spite of consumer skepticism and ignorance and ongoing concerns within the food industry, transgenic agricultural biotechnology is poised to release "a dizzying array of genetic innovations in the years ahead." The consultants asserted that the firms "must first strengthen their capabilities to work effectively with the many stakeholders whose interests are affected by their bio-engineered products... We believe this kind of advocacy, or social marketing, will become a core competency of successful companies." Since this is an attribute of the aforementioned large firms, "research and development activity in this sector is likely to remain highly concentrated," the report concluded.

Of primary importance is the fact that the Starlink and ProdiGene incidents highlight the vulnerability of all food crop production to potential contamination by unwanted proteins from PMP crops. Based on 2001 NCGA (National Corn Growers Association) data, corn production alone in the Midwest is 40% of total world maize production. This is approximately a 9.5-billion bushel (at 2.35/bu \$22.3-billion) per year business at 2003 prices. The consequent additional economic impact for the shipping, processing, food and feed production, and industrial markets, is incalculable.

A central tenant of any successful economic vehicle is that development of new product lines should not threaten the core business profit centers, in this case, non-transgenic conventional corn production. With respect to overall economic return to growers, current PMP production is insignificant in comparison to overall corn production. However, the Starlink and ProdiGene incidents have had enormous impact on food safety awareness, environmental concerns, the scrutiny and increased suspicion of biotechnology companies, and international trade relations. From an economic standpoint, conventional corn production must be safeguarded. Agriculture is at a crossroads, and difficult decisions must be made regarding the paths to future profitability and sustaining farm communities.

With respect to ProdiGene, the company most likely will survive. All fines were paid through profits from their commercialized trypsin product line. In spite of the huge problems caused by those few volunteer corn plants from the 2001 growing season, in 2002 the company grew 600 acres of transgenic corn from Texas to Nebraska, under close scrutiny from the USDA, without a single incident from any of their production fields. However, in light of the BIO recommendation, ProdiGene and other companies may voluntarily not plant in the "heartland." Many firms are choosing to adopt a "wait-and-see" attitude until regulatory and liability standards are more firmly established. Whether this will be adventitious in the long run, or constitute a major set back to Midwestern PMP-agriculture, is anyone's guess.

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**Horan Brothers Specialty Crops.** 3220 240<sup>th</sup> street, Rockwell City, IA, 50579.

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