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Pharmaceuticals and Industrial Products in Crops: Economic Prospects and Impacts on Agriculture

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The Potential Scope of Biomanufacturing

To be clear agriculture has long served to “biomanufacture” a wide array of biomaterials, including compounds used in drugs, stimulants, dietary supplements, flavorings, fillers, lubricants, dyes, adhesives, fuels, and more. Yet, these products are either singularly derived from a specifically cultivated natural source (for example, coffee and natural rubber) or they are essentially by-products from major food crops (for example, lubricants derived from soybean oil). In contrast, with modern biomanufacturing, common crop species can be genetically engineered to synthesize and deliver a broad range of unique biomolecules needed for medical or industrial use. In theory, production of almost any kind of biomolecule could be engineered into plant hosts—including nucleic acids, carbohydrates, oils, and secondary metabolites such as vitamins. However, today most R&D is focused on expressing just a handful of valuable proteins, mostly antibodies, vaccines, enzymes, and other pharmaceutical proteins.

Some indication of the number of genetically engineered biomanufacturing crops moving toward commercialization can be gleaned from data on field-trial permits issued by the USDA. These have increased steadily since the first permit (for production of the enzyme amylase) was granted in 1991 (see Figure 1). A high point was reached in 2000, when over 40 permits were sought. The number of field trials took a big dip in 2002 and 2003, because of industry-wide biosafety concerns following the ProdiGene fiasco (more on this to follow). Fieldwork seems to be picking up again in 2004. At present, we estimate that over 25 permits will be granted this year.

Crop biomanufacturing is attractive because of the potentially large cost savings that could result from using high-yielding and easily cultivated crops. Compared with current fermentation biomanufacturing techniques, crops would have a comparative advantage in both the absolute scale of production and the rate of scalability that could be achieved, resulting in lower cost, faster speed to market, and considerably smaller up-front fixed investments. Other benefits would include purity of the resulting product (with no animal pathogens or cell culture contaminants), ease of storage and transport, and convenience of oral delivery of the product.

The Costs of Risk and Regulation

A major issue with crop biomanufacturing is the potentially large risks that may be involved. The essence of the problem is the reliance on crops that until now have been used exclusively for food or feed to produce bioactive compounds which may, under certain conditions, turn out to be toxins, allergens, or to have hormonal effects. Although grown and handled separately, the possibility arises that these compounds, intended for pharmaceutical or industrial use, could end up in food and feed supplies by accident. There is thus a real, objective risk of direct harm to human health and the environment.

Risk specialist Robert Peterson and plant biologist Charles Arntzen, in the February 2004 issue of Trends in Biotechnology, argue that, while some of these proteins may be quite novel, few are likely to be highly harmful, and any direct food safety risk they pose is both identifiable and manageable. In short, actual harm is highly unlikely. Yet, the indirect risk from such an eventuality could be catastrophic from an economic point of view. An incident could call into question the very integrity of the food supply. The food industry is particularly concerned, and both...
the National Food Processors Association and the Grocery Manufacturers of America have taken strong positions in favor of strict regulation to achieve maximum protection of the food supply (and their members’ brand name products) from possible contamination by PMPs and PMIPs. Indeed, the biotech industry should be extremely concerned as well, as any possible realization of undesirable, unintended effects would be seized upon by an already active anti-biotech lobby and could prove crippling for future biotechnology research.

U.S. regulation in this area is undergoing an extensive (and unfinished) review. Current and interim rules, however, implicitly presume a zero tolerance level for the presence of PMPs and PMIPs in the food supply. Such a strict requirement may be impossible to achieve in practice and may indeed impose unnecessary costs without increasing safety. Given that some of the proteins are known to pose little or no risk, whereas others pose indeterminately or high risk, it would seem sensible to regulate them differently. Regulations that impose zero-tolerance across the board may result in unnecessary precautions for low-risk products while diluting the resources and attention spent on the actual high risks. Yet, the overriding objective of preserving public confidence in the integrity of the food supply may require a stricter, and seemingly less efficient, regulation.

The ProdiGene incident illustrates the potential dangers. In 2002, the USDA found that volunteer corn that was genetically engineered by ProdiGene (a small, privately held biotech company and a leading firm in this technology) to express a vaccine for a viral disease in pigs had contaminated some soybean fields in Nebraska and Iowa. These volunteer plants were left over from field tests carried out (under duly obtained USDA permits) the year before. Despite lack of evidence that such a contamination posed any health risk, the product from these soybean fields (500,000 bushels) was quarantined and eventually destroyed. ProdiGene paid a fine of $250,000 and had to bear the cost of destroying the contaminated product ($3 million). The ensuing financial stress on the company resulted in it being sold to a third party, Stine Seed, in 2003.

To avoid contamination of food and feed by PMPs and PMIPs, a fail-safe containment and segregation program must be put in place. That will necessarily entail use of physical separation between pharmaceutical or industrial crops and conventional feed and food crops. One low-cost spatial segregation solution would be not to grow PMP corn in the Corn Belt. The other logical measure often suggested is simply to use plants other than food and feed crops to produce PMP and PMIPs—tobacco, for example, or even duckweed. It is true that, both at the research stage and at the production stage, it is comparatively easier to use corn as the vector for pharmaceutical and industrial traits than to use, say, duckweed. But such an efficiency advantage may pale in comparison with the potential costs that would arise if high-risk pharmaceutical proteins were to end up in the food chain.

**MARKET IMPACTS AND THE AGRICULTURAL SECTOR**

Demand for biomanufacturing of recombinant proteins is rapidly growing, in both breadth (with more and more new proteins introduced) and depth (with greater volumes demanded of existing proteins). Over one-third of the new drugs approved since 2000 have been therapeutic proteins, with the proportion expected to increase in coming years. Datamonitor estimates annual global sales of therapeutic proteins in final pharmaceutical markets at $30 billion and growing at 20 percent per year; with sales approaching $60 billion by 2010. Antibodies represent the most promising therapeutic market for crop biomanufacturing, as demand is growing particularly fast, and significantly higher quantities are needed. The market for industrial enzymes will be an additional source of demand for biomanufacturing, although it is considerably smaller, at about $2 billion and growing at about 5 percent.

Whether crop biomanufacturing systems can significantly tap this emerging market remains to be seen, as there is significant competition from other sources of biomanufacturing capacity. Today, virtually all recombinant

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Proteins are produced by bacteria, yeast, or mammalian cell lines in closed-vessel fermentation facilities. While they are costly up front, can take several years to build and bring online, and have limited capacity, these methods enjoy the advantage of being familiar to the pharmaceutical industry and they are constantly being improved by new R&D and learning-by-doing. Furthermore, crops are not the only “alternative” platform attempting to enter the market. Biomanufacturing based on other host organisms, including transgenic livestock, algae, and even insect larvae, are being rapidly researched and developed.

Agriculture’s direct contribution to this emerging industry, however, may be limited. While PMPs or PMIPs are highly valued, they often require only a small amount of land to satisfy demand. A recent report by bio-era (a research firm in Cambridge, MA) concludes that, in the next 10 years, an optimistic scenario would be perhaps 25,000 acres, worldwide, devoted to crop biomanufacturing. Even under this rosy scenario, it is apparent that biomanufacturing is not likely to affect many large-scale farming operations.

Furthermore, in an effort to comply with the expected stringent regulation, companies developing these crops are likely to maintain a tight control on the entire production cycle of the products, acquiring land or farm services under contract. And the implicit costs of regulation may induce crop biomanufacturing to locate away from the traditional areas of agricultural production, possibly outsourcing overseas. That is, it is precisely because they have a strong comparative advantage in food and feed production that locations such as Iowa may have a competitive disadvantage in growing PMPs and PMIPs. Ultimately, the returns to agriculture will be for use of the land and for services provided in the growing of the crop, a relatively small contribution to the long process of producing and delivering PMPs and PMIPs to end users.

**Prospects and Limitations**

Whereas the prospects of developing crops genetically engineered to produce pharmaceuticals and industrial products is exciting, there are four major factors that may limit the potential of crop biomanufacturing in the near future. First, both scientifically based risks and perceived risks to the food supply and the environment will drive up costs of regulatory compliance and containment. Considerable fixed-cost investments in land, equipment, and professional expertise will be required to enter the business. Also, the technology’s owners will likely maintain an effective control on the production of such crops in a tightly vertically integrated structure to ensure highly contained growing operations.

Second, the scale of production—while potentially large from the perspective of the biotech industry—is likely to remain quite small by agriculture’s standards. Third, competition from other biomanufacturing platforms will continue to be fierce, as innovation and development of capacity proceeds on all fronts at a rapid pace. Containment risks will always remain much less of an issue for in-vessel fermentation systems than for agriculture, particularly when food crops are involved. Fourth, competition and industrial structure within the crop biomanufacturing sector may keep margins low. Contract structure for the farm-level production stage will likely entail limited opportunities for primary contract growers to capture the value.

It is of course possible that newer biomanufacturing crops or technologies may prove to be exceptions to any of these four factors. For example, high-volume, high-acreage products, such as specialized bio-energy feedstocks or “functional” nutritional ingredients, that require little or no segregation from the food supply may emerge. With such products, of course, major agricultural producing regions will soon compete globally, just as they do in commodity markets today.

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