PRELIMINARY ECONOMIC EVALUATION OF BIOPHARMING IN NEW ZEALAND

William Kaye-Blake, Caroline Saunders, and Louise Ferguson [1]

Agribusiness and Economics Research Unit, Lincoln University
kayeblaw@lincoln.ac.nz; 03 325 2811 extn 8274

Abstract

Biopharming – the production of pharmaceutical compounds in plant and animal tissue in agricultural systems – is touted as the next major development in both farming and pharmaceutical production. This paper summarises the current information available on biopharming and presents a model for understanding its potential impacts. The proponents of biopharming appear to be focused on the potential cost savings from higher productivity, while several other, problematic dimensions of biopharming receive comparatively little attention. A full analysis suggests that biopharming may or may not increase social welfare.

Introduction

Biopharming – the production of pharmaceutical compounds in plant and animal tissue in agricultural systems – is touted as the next major development in both farming and pharmaceutical production. The potential uses of the technology range from functional foods – food products enhanced to provide health benefits – to nutraceuticals – biologically produced compounds intended for sale as supplements – to biopharmaceuticals – compounds that have gone through the full drug testing regime. For farmers, the appeal of biopharming is the production of high-value, niche products, which moves them away from commodity agriculture. For pharmaceutical firms, biopharming promises a method for reducing production costs. For the general public, the benefits of biopharming would be cheaper drugs produced more quickly.

Biopharming is new territory for the agricultural and pharmaceutical industries, and presents novel challenges for government regulators and others, particularly in New Zealand. This paper examines the economics of the opportunities and challenges that biopharming presents. It investigates the research that has been done to this point in order to identify the key economic issues facing the development of biopharming. It also analyses the potential impacts, using a combination of economic theory and prior research. The result is an initial map that can help in charting New Zealand's way in this new territory.

Prior research

Because biopharming has arisen out of a confluence of agriculture, pharmaceutical production, and biotechnology, a number of topics need to be included in a review of prior research. This section first examines the literature that focuses specifically on biopharming. This examination considers the state of the industry and the economic issues that arise with biopharming. These issues then serve as departure points for several subsequent sections, which include the economy of New Zealand, potential economic impacts of genetically modified organisms (GMOs) in New Zealand, overseas research on GMOs, and consumer literature relevant to the economics of biopharming.

Research on biopharming

The current situation in the biopharming industry is difficult to assess. It is a developing industry with a large number of companies entering and exiting. There is nearly no academic literature focused specifically on this industry, either on its structure or its technology. As a result, the economic information comes largely from two sources: the non-academic press and economic information contained in non-economic publications.

Biopharming is one area of a larger industry focused on producing biological compounds of pharmaceutical

[1] This research reported in this paper was part of the Constructive Conversations project, funded by the Foundation for Research, Science and Technology (FRST No. UOCX0221). Joanna Goven, Jack Heinemann, and the rest of the project team have provided a sounding board for ideas and approaches for this analysis. The contributions of these people notwithstanding, the final responsibility for the paper lies with the authors.

interest. In biopharming, these compounds are produced using crop plants or livestock. The plants and animals are genetically modified to produce or express the compounds. The expression may happen in any or all parts of an organism: for example, a maize plant may be modified to express the compound specifically in seeds, or a cow to express the compound in milk. The site of the expression is a key issue, because it affects the costs of production as well as the risks. Thus, tobacco has been pursued as a biopharm crop when expression is in leaf tissue because tobacco produces a large amount of green matter, while maize is useful for compounds produced in seed.

These same compounds may be produced using other non-biopharming technology, however. In fact, according to Elbehri (2005) there are 84 biopharmaceuticals on the market, while Goldstein & Thomas (2004)stated that 'during the last two decades, approximately 95 biopharmaceutical products have been approved by one or more regulatory agencies for the treatment of various human diseases including diabetes mellitus, growth disorders, neurological and genetic maladies, inflammatory conditions, and blood dyscrasias'. All of these biologics, except perhaps one, are produced using non biopharming methods. Instead, they are produced using cell culture, in which vats of modified mammalian or plant cells are grown in containment and are then processed to extract the target compound. There is reference in the literature to one biopharmaceutical being produced using plant biopharming: the compound hirudin, produced in Canada (Giddings, Allison, Brooks, & Carter, 2000). The biopharmaceutical industry output is estimated to have a cumulative market value of US$41 billion, excluding pharma crop processes, with an annual growth rate of 20 per cent (Wisner, 2005). Graff & Moschini (2004) suggested that global sales of therapeutic proteins are $30 billion with sales estimated to approach $60 billion by 2010. The market for industrial enzymes will be at about $2 billion and growing at five per cent per year. Finally, biological compounds such as the above are just one part of the much larger pharmaceutical industry.

Biopharming differs from cell culture methods on several dimensions. The main differences are summarised in Table 1[2]. This table appears to originate with Fischer & Emans (2000), but has been modified and repeated in a number of publications (Goldstein & Thomas, 2004; Kermode, 2006; Ma, Drake, & Christou, 2003; Stoger et al., 2002). The entries in the table indicate that biopharming is better than cell cultures in these ways: storage and distribution is easier and cheaper; gene size is not limited; it has multimeric protein assembly (SigA); production cost is lower; production scale is greater; propagation is easier; protein homogeneity may be higher; protein yield is slightly higher; biopharming is safer; scale-up costs are lower; and less time is required. However, there are issues that make biopharming less attractive than mammalian cell culture: there is a public perception that it entails greater risk; its glycosylation may not be correct; proteins may not fold accurately in transgenic plants; and therapeutic risks from the compounds is unknown.

Looking at this list, the dimensions that appear to be driving the interest in biopharming are largely related to the costs of producing these therapeutic proteins. The widely-cited estimate from Kusnadi, Nikolov, & Howard (1997) is that plant biopharming could produce compounds at one tenth to one fiftieth the cost of currently methods. Cost estimates for plant biopharming range from US$5.50 to US$600 per gram of protein, while estimates for cell culture range from US$50 to US$5000 (Kaye-Blake, Saunders, & Ferguson, 2007). The cost savings are a result of lower costs for the factories that produce the feedstock and purify the compounds. Cellular fermentation facilities require an investment of around $450 million and a time commitment of five to seven years for plant approval and construction, while the purification facilities required for plant biopharming would cost only $80 million and require three to five years to finish (Elbehri, 2005). Related to the lower cost is the greater convenience of scaling production up or down. With biopharming, more feedstock for the purification can be produced by growing more plants or animals, and creating more purification facilities is cheaper and less time consuming. Thus, creating more or less of a compound is easier than with current methods.

Whether this cost comparison describes the actual situation or rather biopharming's potential is unclear. The comparison has been repeated in one form or another in a variety of publications. However, commercial plant biopharming is not a current reality (again, with one exception), so there is likely to be an element of speculation in these figures. The one comparison of actual costs that was available for this research was that biotech company Agennix claimed that it could produce lactoferrin using cell culture methods at a cost comparable to Ventria Bioscience's biopharmed rice (Wisner, 2005).

A further point raised in the above comparison of production methods is that the compounds produced through biopharming, in particular plant biopharming, are not exactly like those produced in cell culture/fermentation. These cost calculations, therefore, appear to presume that the technical issues facing biopharming, such as glycosylation or protein folding,

[2] The information in the table is repeated here without critical assessment. That is, the authors of the present economic report do not pretend to have the expertise to assess whether, for example, the protein folding in crop plants is different than protein folding in mammalian cell culture, or one method is 'safer' than another. Each of these dimensions could be further discussed, researched, and contested. The information is presented here in order to highlight that the literature on biopharming suggests that the differences between different methods of producing commercial biologic compounds are many and complex.

Table 1: Comparison of features of recombinant protein production in plants, animals, yeast and classical systems

	Transgenic Plants	**Plant Viruses**	**Yeast**	**Bacteria**	**Mammalian Cell cultures**	**Transgenic Animals**
Cost/storage	Cheap/RT	Cheap/-20ºC	Cheap/-20ºC	Cheap/-20ºC	Expensive/N2	Expensive
Distribution	Easy	Easy	Feasible	Feasible	Difficult	Difficult
Gene size	Not limited	Limited	Unknown	Unknown	Limited	Limited
Glycosylation	'Correct'?	'Correct'?	Incorrect	Absent	'Correct'	'Correct'
Multimeric protein assembly (SIgA)	Yes	No	No	No	No	Yes
Production cost	Low	Low	Medium	Medium	High	High
Production scale	Worldwide	Worldwide	Limited	Limited	Limited	Limited
Production vehicle	Yes	Yes	Yes	Yes	Yes	Yes
Propagation	Easy	Feasible	Easy	Easy	Hard	Feasible
Protein folding accuracy	High?	High?	Medium	Low	High	High
Protein homogeneity	High?	Medium	Medium	Low	Medium	Low
Protein yield	High	Very high	High	Medium	Medium-high	High
Public perception of 'risk'	High	High	Medium	Low	Medium	High
Safety	High	High	Unknown	Low	Medium	High
Scale up costs	Low (unlimited biomass)	Low	High**	High**	High**	High
Therapeutic risk*	Unknown	Unknown	Unknown	Yes	Yes	Yes
Time required	Medium	Low	Medium	Low	High	High

* - residual viral sequences, oncogenes, endotoxins; ** - large, expensive fermenters etc; ? – unclear.

Source: (Fischer & Emans, 2000).

have been overcome. The cost calculations indicating large cost savings through plant biopharming are in effect comparing the costs of producing two different compounds. This idea will be formulated more explicitly below.

One peer-reviewed analysis of the economics of biopharming has been published (Kostandini, Mills, & Norton, 2006). It focused on the production of human serum albumin (HSA) in tobacco as a case study for biopharming. The market for HSA was modelled with linear supply and demand functions, and the results of a price reduction on the market were estimated both when the producer had monopoly power due to its innovation and when it did not. In the first case, the innovation resulted in excess (monopoly) profits for the firm. It did not benefit consumers, however. In addition, tobacco farmers were either unaffected or left worse off; they provided the tobacco at cost as a result of the relative market power of the farmers and the innovating firm. The latter case, without the monopoly, is assessed as unrealistic: the firm would not pursue the innovation unless it could secure monopoly pricing power. This modelling suggests that control of the innovation is important, and that widespread welfare gains from biopharming may be unlikely.

The main idea that falls out of this discussion is that biopharming is still in a research stage; it is not a developed industry with commercial products and commercial revenue. Thus, the valuations of products and companies are not based on market transaction for final products. Instead, those valuations are based on projections of the future market value to be realised from present research.

Research on GMOs

While biopharming promises to revolutionise production of pharmaceuticals, there are elements of the industry that suggest comparisons with other areas of research. In particular, the production of pharmaceutical compounds using biopharming relies on genetic modification to engineer the production of the novel compounds; the plants and animals used in biopharming are genetically modified organisms (GMOs). Thus, to understand the potential impact of introducing biopharming, one can examine the literature on economic impacts of GMOs.

There have been several macroeconomic analyses of the potential impacts of GMOs on New Zealand. Some of these resulted from the Royal Commission on Genetic Modification. A number of submissions came from entities with economic interests in GM, either for or against (Nana, 2000; Stroombergen, 2000; Wright, 2000), but the economic research was remarkably thin (Campbell et al., 2003). An important lesson from this modelling was the importance of accurate and transparent assumptions for modelling. Another economic analysis presented to the RCGM was based on the Lincoln Trade and Environment Model (LTEM) (Saunders & Cagatay, 2001). The results of the scenarios in which New Zealand adopted GM crops were generally negative for NZ, even when a preference for GM products and/or increased productivity was modelled (Saunders & Cagatay, 2001). Further modelling work has in general supported these conclusions (Saunders, Kaye-Blake, & Cagatay, 2003).

Further research has explored the dynamic interaction of consumer willingness to pay for premium products and the impacts of productivity on farmers' returns. Kaye-Blake, Saunders and Fairweather (2004) estimated the maximum gains that were possible from producing crops which commanded a premium. They found that growers of the most favoured GM product, anti-oxidant apples, would be able to charge a 17 per cent premium to 26 per cent of the apple market, leading to an average increase in industry revenues of 4.3 per cent. Anti-oxidant apples are an example of a functional food, so these findings are relevant for biopharming broadly defined.

Another source of economic analysis of GM crops in NZ is a report that the Ministry for the Environment (MfE) commissioned from Business and Economic Research Limited (BERL) and the AERU (Sanderson et al., 2003). The report found that the overall effect on GDP from commercial use of GMOs in agriculture could be either negative or positive, depending on how consumer reactions affect actual trade and how GM technology affects actual production. Research conducted to inform the economic modelling for the MfE report provided new information on how overseas consumers' reactions. The survey research found that 27 per cent of Australians, 20 per cent of US citizens, and 30 per cent of Britons were opposed to the use of GMOs. In addition, nine per cent of Australians, five per cent of US citizens, and six per cent of Britons would stop visiting New Zealand if a GMO were released in the country.

International research has also simulated the macroeconomic impacts of GMOs. For example, Moschini, Lapan, & Sobolevsky (2000) found that U.S. farmers were better off when they had access to cost-reducing technology that was not available in other countries. However, they were worse off if the technology increased their yields, and they did not gain nearly as much if other countries also adopt the technology. In other work, Jackson & Anderson (2003) found that Australasia gained when other countries banned GM products because they produced the favoured non-GM crops.

Actual impacts of the adoption of GM crops have been studied, too. The Tokyo Grain Exchange, for example, provides trading in futures contracts for non-GM soybeans. The premium over a standard contract is approximately the same as segregation costs (Parcell, 2001), suggesting that whilst there is a premium there

are no excess profits for non-GM soybeans. Similar premiums are reported in Europe (USDA, 2001).

Another topic that has been extensively studied is consumer reactions to GMOs. New Zealand research has assessed consumer reactions in a number of ways. Atitudes and perceptions of New Zealanders have been studied by social scientists at two Crown Research Institutes. One report found that women are less sanguine about GM food than men, and that a product that is itself modified is less acceptable than a non-modified product produced using GM (Gamble & Gunson, 2002). Another paper found somewhat less support in New Zealand than the above research; however, a majority of respondents were willing to support GM food in some circumstances (Small, Wilson, & Parminter, 2002).

Peer-reviewed research has also examined consumer reactions to genetically modified food. Kassardjian, Gamble, & Gunson (2005) found that 28 per cent of participants were not interested in the GM apples, while the majority was willing to pay between NZ$0 and NZ$0.50 extra for apples providing either environmental or health benefits. Kaye-Blake, Bicknell, & Saunders (2005) found that a significant minority of consumers were not interested in GM apples. For some who were willing to buy GM apples, the price reductions were quite large, while for other respondents the price reductions were not statistically significant from zero. Thus, both of these articles suggest that a majority of consumers are willing to buy GM food, but that the prices demanded by these consumers have a considerable range.

International consumer research has several general findings of interest. First, broadly speaking, medical uses of biotechnology are more acceptable than food uses, and biotechnology focused on plants is more acceptable than animal biotechnology or plant-animal genetic transfers (Campbell et al., 2003). Secondly, risk perceptions regarding biotechnology are complex. Fischhoff & Fischhoff (2001) and Gaskell et al. (2004) have suggested that risks and benefits are not combined into a unidimensional scoring of the value of the technology, but that they act as thresholds in individuals' decision-making processes. Thirdly, people are not simply 'for' or 'against' GM *per se*, but evaluate the technology in different ways (Marris, Wynne, Simmons, & Weldon, 2001). Individuals often express ambivalence about GM technology (Gaskell et al., 2003; Marris, Wynne, Simmons, & Weldon, 2001).

Finally, environmental values seem to cut both ways. To the extent that biotechnology may represent a perceived threat to the environment, some consumers may see it as a negative development. To the extent that biotechnologies are perceived to reduce environmental damage, they may become more valuable. Researchers have found that favourable attitudes towards nature are correlated with negative attitudes towards GM (Bredahl, 2001). More specifically, survey respondents did not agree that GM is environmentally friendly (Small, Wilson, & Parminter, 2002), and ecocentric respondents did not support GM (Siegrist, 1998). On the other hand, surveys that attribute environmental benefits to biotechnology in agriculture find positive reactions. Consistently, respondents express more support for biotechnology applications that have an environmental benefit than for applications that do not (IFIC, 2002; Macer, 1994; Sheehy, Legault, & Ireland, 1998).

The New Zealand economy

The paper now turns to a discussion of the economy of New Zealand. In assessing the potential impacts of introducing biopharming to the country, it is important to understand the current economy.

New Zealand is widely recognised as having an economy with a strong foundation in biology and the environment. It is precisely in these areas that some of the largest impacts of biopharming may be felt. Economic impacts from biopharming are thus likely to affect predominantly the industries that rely on the country's natural resources: agriculture and tourism.

The primary sector is an important contributor to the New Zealand economy, both to Gross Domestic Product (GDP) and to export earnings. Together, agriculture, forestry, and their associated sectors contributed 18 per cent of the country's GDP in 2002/03 (Ministry of Agriculture and Forestry, 2005). In addition, agricultural and silviculture exports accounted for over 60% of merchandise exports (Ministry of Agriculture and Forestry, 2005).

It is possible to disaggregate the exports from different parts of the agricultural sector using data from *New Zealand External Trade Statistics* from the Ministry of Foreign Affairs and Trade. Table 2 is based on statistics from 2002.

The tourism industry is another important part of the New Zealand economy. The Tourism Satellite Account (Statistics New Zealand, 2006), which calculates the contribution of tourism to the New Zealand economy, showed a total tourism expenditure of $17.5 billion for the year ending March 2005, contributing nine per cent of gross domestic product. International tourism expenditure accounted for 18.7 per cent of total national export earnings and 10.5 per cent ($526m) of GST receipts in 2005 (Ministry of Tourism, 2006).

Research confirms that tourists have a 'clean and green' image of New Zealand and that they are inclined to visit because of the unpolluted nature and beautiful landscapes (PA Consulting Group, 2001; Sanderson et al., 2003). A survey of international tourists in New Zealand and individuals in New Zealand's main overseas tourism markets indicated that they perceive the New Zealand environment to be above average and among the best in the world (Sanderson et al., 2003).

Research conducted by TNZ and Colmar Brunton (New Zealand Tourism Board, 1995, 1997) also shows that it is the tourists' perception of the clean and green environment in New Zealand that motivates them to visit. Tourists are attracted to the beautiful scenery and landscapes, and the opportunity to engage in nature-focused experiences (PA Consulting Group, 2001).

New Zealand's economy has a significant portion that is based on natural resources. The agricultural sector depends on the biological resources to produce not only food and fibre for the domestic population but also for a large percentage of the country's exports. International tourism also depends on the country's natural resources, its biology and landscape, and adds significantly to the country's export earnings. Tourism exploits New Zealand's image as a clean and green destination.

Biopharming also depends on natural resources, and is thus a potentially competing claim on these resources.

Table 2. New Zealand Export Statistics

Main export markets	Value (million NZ$)
Australia	5,694
United States of America	4,793
Japan	3,698
United Kingdom	1,525
Republic of Korea	1,450
People's Republic of China	1,419

Main export products	Value (million NZ$)
Dairy	5,925
Meat	4,423
Wood	2,371
Fish	1,401
Starch, Casein	1,386
Fruit (7^{th} ranked)	1,156
Vegetables (15^{th} ranked)	447

Main exports by market	Value (million NZ$)
Australia	
Dairy	300
Meat	26
Wood	380
Fruit and Vegetables	215
United States of America	
Dairy	994
Meat	1,316
Wood	494
Fruit and Vegetables	154
Japan	
Dairy	551
Meat	253
Wool	600
Fruit and Vegetables	387
United Kingdom	
Dairy	229
Meat	540
Wood	2
Fruit and Vegetables	175

Whether the net impact on the New Zealand economy is positive, negative, or neutral depends on the ability of these different industries to use the resources productively. It also depends on potential externalities and how large those effects are.

Theory of Impacts

Supply impacts

The essential supply question for biopharming is what will happen when the industry moves from a situation of 84 biopharmaceuticals (Elbehri, 2005) on the market being produced in contained cell culture at a price of about $1000 per gram to a situation in which therapeutic proteins are produced through biopharming at a cost of, for example, $50 per gram. It is possible to represent this change with a model. In this model, the cost of producing a compound is directly related to the characteristics of that compound; each compound may be viewed as a bundle of characteristics. If each characteristic is viewed as discrete, then it is possible to assign a cost to each one. The total cost of each compound is thus a function of the costs of the characteristics and the amount or level of the characteristics in each compound. For example, a biologic compound can be considered as a vector of characteristics (Fischer & Emans, 2000; Goldstein & Thomas, 2004; Kermode, 2006; Ma, Drake, & Christou, 2003; Stoger et al., 2002):

> [Cost/storage, Distribution, Gene size, Glycosylation, Multimeric protein assembly, Production cost, Production scale, Production vehicle, Propagation, Protein folding accuracy, Protein homogeneity, Protein yield, Public perception of risk, Safety, Scale-up costs, Therapeutic risk, Time required, Uncertainty].

A biologic compound could be produced using mammalian cell culture, which is current technology, or can be produced using biopharming. Using cell culture, the cost of the compound could be:

$C_{cc} = \boldsymbol{\beta}_n * \mathbf{k}_{cc} = 1000$ dollars per gram,

where C is the cost, cc denotes cell culture technology, $\boldsymbol{\beta}$ represents the vector of costs of the characteristics, n is the number of characteristics, and $\mathbf{k}$ denotes the characteristics identified above. The sum of the characteristics multiplied by their costs is equal to the total cost of production. Using biopharming, the cost is estimated to be:

$C_b = \boldsymbol{\beta}_n * \mathbf{k}_b = 50$ dollars per gram,

where b denotes biopharming and all other terms are as defined above. The values for the βs are constant across the technologies, weighted for each compound by the associated level of k. In principle, if the levels

are known and given the prices of different compounds produced in different ways, it would be possible to estimate βs. However, they are largely notional, used to create a model for approaching the economics of the issue.

The economics can be shown as follows. The adoption of biopharming entails a movement from cell culture to biopharming. The cost shifts from $1000 per gram to $50 per gram. There are also associated changes in the levels of many characteristics. This may be summarised as follows (Fischer & Emans, 2000; Goldstein & Thomas, 2004; Kermode, 2006; Ma, Drake, & Christou, 2003; Stoger et al., 2002):

$C_{cc} - C_b = 1000 - 50 = \boldsymbol{\beta}_n * (\mathbf{k}_{cc} - \mathbf{k}_b)$

The benefit of this approach is to help ultimately to understand the specific differences between production methods and consider how those differences contribute to the cost differences from biopharming.

Imperfect competition

The cost of developing a biopharmaceutical has been estimated at US$1.2 billion (DiMasi, forthcoming). This amount pays for the technical development as well as moving the compound through successful clinical trials and securing regulatory approval for the compound. It is a fixed cost borne by the owner of the technology, a cost that must be recouped in order for a biopharmaceutical to be profitable. However, economic theory focuses on the marginal cost of production as the main determinant of market price; fixed costs, particularly sunk costs, do not figure in calculations of marginal costs and thus price in a competitive market.

In order to allow the developer the opportunity to recoup these fixed costs, the government grants a temporary monopoly in the form of a patent. A monopoly reduces net social welfare by constraining supply of a product and raising its price. However, in the absence of an ability to raise the price of a biopharmaceutical above its marginal cost of production, the developer would not be able to recoup the development costs. If developers could not recoup these costs, they would cease to invest in developing new biopharmaceuticals. Thus, the granting of patents provides an incentive to invest in research and development that can be profitable over the medium term. Whether this arrangement leads to maximum social benefit can be debated, but it is the current system in which biopharming would operate.

To complicate the analysis of biopharmaceuticals, the situation in the industry is more like an oligopoly than a monopoly. In a monopoly, there is one supplier of the product. In an oligopoly, several firms sell products that are more or less similar. These firms may compete on price, quantity, or product qualities, depending on the specific model of oligopoly. Biopharming, as discussed above, is pursuing the production of existing pharmaceutical compounds but in a novel way. Thus, the product itself is potentially not unique. If it is not unique, then firms appear to be engaged in an oligopolistic competition based on price with potentially weakly differentiated products. The theoretical issue is complicated by the issue that the innovating firm has rights to a production technology that is potentially more efficient than its competitors. This issue suggests that competition could be price-based, but does raise the potential for excess profits as a result of the proprietary technology.

Demand for biopharming products

An important consideration is the impact of biopharming on the rest of New Zealand's agricultural and tourism industries. This depends on consumers in overseas markets. Some of the specific issues are: size of consumer segments; estimates of market size, given current purchases of agricultural products and consumer scepticism regarding biotech; and price impacts, again given current commodity prices, price trends, and consumer perceptions. These issues have been identified in prior research, and were discussed above. It is important to recognise, however, that consumer demand may be affected at several levels: for the pharmaceutical, for the host crop, for the industry, and even for other New Zealand products.

Risk and uncertainty

Special consideration should be given to the idea of uncertainty. The uncertainty identified in the literature is technical, regulatory, and political. If the foregoing review has highlighted anything, it is that the economic impacts of commercial release of biotech products are uncertain and potentially very complex. The uncertainty and complexity make identifying risk evaluation criteria difficult. The following discussion should be seen in this light and should not be taken as exhaustive or predictive.

One way to think of risk is as the probability of an occurrence multiplied by its size or importance. This characterisation has been demonstrated to be incomplete, especially when discussing perceptions of risk (see, for example, Slovic, 2000). This incomplete formula is adopted here only as a starting point.

The second mental construct to consider is concentric circles (we are indebted to Tere Satterfield, Decision Research, for this observation). Each product, each crop, can be thought of as the centre of a set of concentric circles moving outward from related crops to the particular agricultural sector to wider categories up to the level of national effects.

In evaluating the risk posed by a particular application of genetic technology, it will be important to consider

the probability of adverse reactions and the value of the sectors affected. Adverse reactions can come in different forms. For example, it may be that consumer reactions to a product are quite strong. On the other hand, the reaction might come from market gatekeepers, regardless of direct consumer reaction. Reactions in one market might be non-existent, but strong in another. The value of the sectors potentially affected is also hard to determine beforehand. A specific product is contained in many concentric circles, and although a biotech product may be intended for restricted use, it may be related or linked to products of much wider commercial importance.

In addition, there is a body of research on risk perception that is outside the economic expertise of the authors. Briefly, risks are perceptually evaluated not just on a 'probability times size' basis, but also on criteria such as control, dread, equity, certainty, voluntariness, etc. These perceptions of risk affect consumers and researchers alike.

Analysis of Potential Impacts

Production through biopharming

The model set out earlier requires data to be estimated. The data that are available are not numbers, but descriptors. From the literature, the difference in cell culture and biopharming as method of production can be stated as follows:

= **β**[	Cost/storage:	Expensive	→	Cheap
	Distribution:	Difficult	→	Easy
	Gene size:	Limited	→	Not limited
	Glycosylation:	Correct	→	Correct?
	Protein assembly:	No	→	Yes
	Production cost:	High	→	Low
	Production scale:	Limited	→	Worldwide
	Production vehicle:	0		
	Propagation:	Hard	→	Easy
	Protein folding accuracy:	High	→	High?
	Protein homogeneity:	Med.	→	High?
	Protein yield:	Med-high	→	High
	Risk perception:	Medium	→	High
	Safety:	Medium	→	High
	Scale-up costs:	High	→	Low
	Therapeutic risk:	Yes	→	Unknown
	Time required:	High	→	Medium
	Uncertainty:	Current	→	Unknown].

The difference vector indicates that the biopharmed compounds are different to the cell culture compounds on nearly every dimension investigated. The differences fall into several categories. The first category is those dimensions that are cost-related and quantifiable, e.g., production cost and protein yield. Biopharming tends to outperform cell culture on most of these dimensions. Biopharming's success on these criteria appears to be driving the cost estimates that biopharmed compounds will be one-twentieth or less of the cost of current production techniques. The second category is those dimensions in which the results of biopharming are unknown. In the difference vector, these dimensions are those with a question mark (?) or labelled 'unknown', such as protein folding accuracy and protein homogeneity. A third category contains those dimensions whose values are known but qualitative. Because the differences are expressed qualitatively, there is insufficient information to generate an economic analysis. Thus, it is difficult to put on value on 'medium' safety versus 'high' safety. Finally, the risk profile of biopharming is, according to the difference vector, a potential concern. One risk dimension, public perception of risk, is worse for biopharming than for cell culture. The other risk dimension, therapeutic risk, is unknown.

The result of this model of biopharming, in which production is viewed as a bundle of dimensions with independent contributions to the cost of production, is that current information is insufficient. Some dimensions, particularly the quantitative cost dimension, have received attention and are favourable for biopharming. Other dimensions are still largely qualitative and even unknown. Finally, there is insufficient information to determine the values of the betas, which indicate the contribution of each dimension to the final price of the compound. That is, the monetary impact of, for example, glycosylation versus worldwide distribution capacity is undetermined. As a result, the full cost of commercialised biopharmed therapeutic proteins, taking into account the technical differences, risks, and uncertainties, cannot be properly estimated from current data.

In addition, this model applies only to the biopharming product itself; it does not account for the concentric rings of influence into other industries. The theoretical model and other economic theory are applied below to an example: the production of lactoferrin in milk.

Lactoferrin in milk

Lactoferrin is a protein produced by mammals and found in milk and even tears (www.pharming.com). It is a product that has considerable health benefits including positively affecting the immune system, proven ability to fight bacteria that cause eye and lung infections and limiting cancer growth in cells. There is still research being conducted on further benefits that could be provided by lactoferrin.

The world market for lactoferrin in 2004 was 90 metric tonnes per year and appears to be growing in global interest (AP-foodtechnology.com, 2004). The reported price for lactoferrin is at least US$300 per kilogram, making the worldwide market valued at approximately US$27 million per year. Fonterra reported that it is participating in the lactoferrin market with a new plant in Hautapu (Fonterra, 2005).

Presently, lactoferrin is extracted from cow's milk and added to food products, such as infant formula and yoghurt. Research has pursued producing a human version of lactoferrin in non-human organisms. The resulting product could be a functional food, nutraceutical, or biopharmaceutical, depending on how much the developing firm invests in following the regulatory process. Also, as a GMO product, it may require labelling.

Biopharming research has produced recombinant human lactoferrin (rhLF) in rice by Applied Phytologics and Ventria Bioscience. The company Agennix has announced that its microbial fermentation processes can produce lactoferrin too, and has production costs that were equal to the Ventria Bioscience biopharm rice (Wisner, 2005). Meristem Therapeutics and Washington State University have also done research on lactoferrin production, but it is unclear as to the exact organisms used. Other research has produced rhLF in the milk of cows and mice (van Berkel et al., 2002).

Scientific research on rhLF provides information relating to some of the dimensions discussed above (Thomassen, van Venn, van Berket, Nuijens, & Abrahams, 2005; van Berkel et al., 2002). The protein structure appears similar to natural human lactoferrin (hLF) (Thomassen, van Venn, van Berket, Nuijens, & Abrahams, 2005). The rhLF and hLF appear to be functionally similar, and to be safe in animal trials (van Berkel et al., 2002). The rhLF is also expressed at high concentration in cows' milk (van Berkel et al., 2002). This research thus seems to have determined that rhLF is physically similar to hLF, and that the protein yield may be commercially sufficient. Some dimensions for which information did not appear available and which are therefore continuing sources of uncertainty are: production cost, production scale, production vehicle, public perception of 'risk', scale up costs, time required.

A further issue with rhLF is that this scientific research has compared the human and recombinant human versions. From a business perspective, however, the comparison of bovine lactoferrin and rhLF is also germane. These two types of lactoferrin could be competing products in the marketplace. It is thus important to know whether the rhLF has any therapeutic benefits over the bovine version, and what the comparative costs of producing it are. One central question is the cost-benefit assessment of the two products. The information available is insufficient to make this assessment.

Furthermore, the rhLF has the further complication of the uncertainty surrounding consumer reactions to GM technology. If there are no adverse reactions, then the simple cost-benefit analysis suggested above would be sufficient to assess the business case. However, the research reviewed above indicates that there are adverse consumer reactions; the question thus becomes the extent and longevity of these reactions. Using the figures cited earlier regarding adverse reactions to GMOs (Sanderson et al., 2003) (27 per cent of Australians, 20 per cent of US citizens, and 30 per cent of Britons opposed to the use of GMOs) and figures on exports from 2002, the potential losses in these three markets from consumer rejection of New Zealand dairy products because of the introduction of a GMO into the dairy sector are NZ$348.5 million per year. This figure does not include any price discounts that other consumers might demand, markets other than those three countries, or exports other than dairy products.

A similar calculation can be made of impacts on tourism. The same research found that nine per cent of Australians, five per cent of US citizens, and six per cent of Britons would stop visiting New Zealand if a GMO were introduced into the environment. Using tourism spending figures for these countries from the New Zealand Tourism Board, the potential losses in tourism amount to NZ$191.1 million per year.

This analysis suggests several things. First, all the necessary business information to assess the economic potential of producing recombinant human lactoferrin in milk in New Zealand is not available. Any assessment at this stage is necessarily preliminary. Secondly, it will be difficult to earn more than an economically normal profit by developing and marketing rhLF. There seem to be several close substitutes and competing technologies, so there appears to be little opportunity to create a dominant position in the market and earn oligopoly or monopoly profits. Finally, social science research suggests that introducing a GMO into the New Zealand dairy sector has a potential to cause a minimum of NZ$539.6 million in losses to the dairy and tourism industries. Thus, such a biopharming endeavour would need to offset those losses before it could be viewed as a net positive for the New Zealand economy. Given that sales of lactoferrin are currently in the tens of millions of US dollars, offsetting hundreds of millions of NZ dollars of lost exports seems unlikely in the short to medium term.

Conclusion

This paper has presented preliminary research into the economics of biopharming. The research has covered a range of economic theory and sources of data. The main reason to cover so much ground is that definitive information on the economics of biopharming is scant. Thus, this research has looked to economic theories of supply and demand, consumer behaviour, and industry structure; assessments of the impacts of prior biotechnologies; and the information that is available on biopharming. All of these elements together underpin the present assessment of biopharming.

This paper has organised its assessment around a model or framework derived from the literature on biopharming. The potential impacts of biopharming are a function of the benefits and costs from changing from

one type of production system to another, coupled with product advantages that the new system might afford. Clearly, there are a number of dimensions on which production systems differ. The impact of biopharming in its broad sense, including biopharmaceuticals, nutraceuticals, and functional foods, depends on how each of these dimensions changes and how those dimensions contribute to the value of the products.

This paper has also illustrated the use of the model with the example of producing lactoferrin in cow's milk. The main result from this examination is that the necessary information to develop a robust economic analysis of these products is lacking. Much of the information on the relevant dimensions is simply unknown. A second result is that the overall economic impact depends critically on reactions in overseas markets. The future impact of consumer concerns is uncertain and contested. Nevertheless, since available information on adverse reactions suggests that the economic impact could be large compared to earnings from novel products, it is important to understand these potential reactions.

This has been a preliminary piece of research. As more information becomes available on the potential products, the economics of their production, and consumer demand for them, this area of research will be able to improve the estimates of the economic impacts of biopharming in New Zealand.

References

Bredahl, L. (2001). Determinants of consumer attitudes and purchase intentions with regard to genetically modified foods -- results of a cross-national survey. *Journal of Consumer Policy, 24*, 23-61.

Campbell, H., Plummer, C., Kaye-Blake, W., Saunders, C., Kitto, L., Polson, C., et al. (2003). Appendix 1: Background literature review. In K. Sanderson, C. Saunders, G. Nana, A. Stroombergen, H. Campbell, J. Fairweather & A. Heinman (Eds.), *Economic risks and opportunities from the release of genetically modified organisms in New Zealand (Report to the Ministry for the Environment)*. Wellington, New Zealand.

DiMasi, J. A. (forthcoming). The Cost of Biopharmaceutical R&D: Is Biotech Different? *Managerial and Decision Economics*.

Elbehri, A. (2005). Biopharming and the food system: examining the potential benefits and risks. *AgBioForum, 8*(1), 18-25.

Fischer, R., & Emans, N. (2000). Molecular farming of pharmaceutical proteins. *Transgenic Research, 9*, 279-299.

Fischhoff, B., & Fischhoff, I. (2001). Publics' opinions about biotechnologies. *AgBioForum, 4*(3&4).

Fonterra. (2005). *Annual Report 04/05*. Auckland, New Zealand: Fonterra.

Gamble, J., & Gunson, A. (2002). *The New Zealand public's attitudes regarding GM food: May and October 2001 - Full Report*. Auckland, NZ: HortResearch.

Gaskell, G., Allum, N. C., Bauer, M. W., Jackson, J., Howard, S., & Lindsey, N. (2003). *Ambivalent GM nation? Public attitudes to biotechnology in the UK, 1991-2002* (Life Sciences in European Society Report): London School of Economics and Political Science.

Gaskell, G., Allum, N. C., Wagner, W., Kronberger, N., Torgersen, H., Hampel, J., et al. (2004). GM foods and the misperception of risk perception. *Risk Analysis, 24*(1), 185-194.

Goldstein, D. A., & Thomas, J. A. (2004). Biopharmaceuticals derived from genetically modified plants. *QJ M: An International Journal of Medicine, 97*(11), 705-716.

IFIC. (2002). Support for food biotechnology holds with increased recognition of benefits: International Food Information Council.

Jackson, L. A., & Anderson, K. (2003, 12-14 June). *Why are US and EU policies toward GMOs so different? Estimating intra-national distributive impacts using GTAP*. Paper presented at the 6th Annual Conference on Global Economic Analysis.

Kassardjian, E., Gamble, J., & Gunson, A. (2005). A new approach to elicit consumers' willingness to purchase genetically modified apples. *British Food Journal, 107*(8), 541-555.

Kaye-Blake, W., Bicknell, K., & Saunders, C. (2005). Process versus product: which determines consumer demand for genetically modified apples? *Australian Journal of Agricultural and Resource Economics, 49*(4), 413-427.

Kaye-Blake, W., Saunders, C., & Fairweather, J. (2004). *Modelling the trade impacts of willingness to pay for genetically modified food* (Research Report No. 270). Canterbury, New Zealand: Agribusiness and Economics Research Unit (AERU), Lincoln University.

Kermode, A. R. (2006). Plants as factories for production of biopharmaceutical and bioindustrial proteins: lessons from cell biology. *Canadian Journal of Botany, 84*(4), 679-694.

Kostandini, G., Mills, B. F., & Norton, G. W. (2006). The potential impact of Tobacco Biopharming: The case of Human Serum Albumin. *American Journal of Agricultural Economics Association, 88*(3), 671-679.

Ma, J. K.-C., Drake, P. M. W., & Christou, P. (2003). The production of recombinant pharmaceutical proteins in plants. *Nature Reviews Genetics, 4*, 794-805.

Macer, D. (1994). *Bioethics for the people by the people*. Christchurch, N.Z.: Eubios Ethics Institute.

Marris, C., Wynne, B., Simmons, P., & Weldon, S. (2001). *Public perceptions of agricultural biotechnologies in Europe*: Commission of European Committees.

Ministry of Agriculture and Forestry. (2005). *Situation and outlook for New Zealand agriculture and forestry*. Wellington.

Moschini, G., Lapan, H., & Sobolevsky, A. (2000). Roundup Ready soybeans and welfare effects in the soybean complex. *Agribusiness, 16*(1), 33-55.

Nana, G. (2000). Witness brief, Royal Commission on Genetic Modification. Wellington, New Zealand.

New Zealand Tourism Board. (1995). *Product Development Opportunities for Asian Markets*.

New Zealand Tourism Board. (1997). *Product Development Opportunities for European and North American Markets*.

PA Consulting Group. (2001). *Valuing New Zealand's Clean Green Image* (Report prepared by S. Thornton, S. Paul and G. Kerr). Wellington, NZ: PA Consulting.

Parcell, J. L. (2001). An initial look at the Tokyo Grain Exchange non-GMO soybean contract. *Journal of Agribusiness, 19*(1), 85-92.

Sanderson, K., Saunders, C., Nana, G., Stroombergen, A., Campbell, H., Fairweather, J., et al. (2003). *Economic risks and opportunities from the release of genetically modified organisms in New Zealand* (Report to the Ministry for the Environment). Wellington: Ministry for the Environment.

Saunders, C., & Cagatay, S. (2001). *Economic analysis of issues surrounding commercial release of GM food products in New Zealand* (Commerce Division Discussion Paper No. 94): Lincoln University.

Saunders, C., Kaye-Blake, W., & Cagatay, S. (2003). *Economic impacts on New Zealand of GM crops: result from partial equilibrium modelling* (Research Report No. 261). Canterbury, NZ: Agribusiness and Economics Research Unit, Lincoln University.

Sheehy, H., Legault, M., & Ireland, D. (1998). Consumers and biotechnology: a synopsis of survey and focus group research. *Journal of Consumer Policy, 21*, 359-386.

Siegrist, M. (1998). Belief in gene technology: the influence of environmental attitudes and gender. *Personality and Individual Differences, 24*(6), 861-866.

Slovic, P. (2000). *The perception of risk*. London, U.K.: Earthscan Publications.

Small, B. H., Wilson, J. A., & Parminter, T. (2002). *Clean, green and healthy? Genetically engineered food: a perceived threat to New Zealand's brand image*. Hamilton, New Zealand: AgResearch.

Statistics New Zealand. (2006). *Tourism Satellite Account: 2005*. Wellington, New Zealand.

Stoger, E., Sack, M., Perrin, Y., Vaquero, C., Torres, E., Twyman, R. M., et al. (2002). Practical considerations for pharmaceutical antibody production in different crop systems. *Molecular Breeding, 9*, 149-158.

Stroombergen, A. (2000). Witness brief, Royal Commission on Genetic Modification. Wellington, New Zealand.

Thomassen, E. A. J., van Venn, H. A., van Berket, P. H. C., Nuijens, J. H., & Abrahams, J. P. (2005). The protein structure of recombinant human lactoferrin produced in the milk of transgenic cows closely matches the structure of human milk-derived lactoferrin. *Transgenic Research, 14*, 397-405.

USDA. (2001). *Demand for certified non-biotech soybean meal expands in the EU* (International Agricultural Trade Report). Washington, DC, US: Commodity and Marketing Programs, Foreign Agricultural Service, United States Department of Agriculture.

van Berkel, P. H. C., Welling, M. M., Geerts, M., van Veen, H. A., Ravensbergen, B., Salaheddine, M., et al. (2002). Large scale production of recombinant human lactoferrin in the milk of transgenic cows. *Nature Biotechnology, 20*, 484-487.

Wisner, R. (2005). *The economics of pharmaceutical crops: potential benefits and risks for farmers and rural communities*. Cambridge, MA, USA: Union of Concerned Scientists.

Wright, J. C. (2000). *The economics of genetic modification* (background paper). Wellington, New Zealand: Royal Commission on Genetic Modification.

JEL Classification
O13, I19, Q16

Keywords
biopharming, New Zealand, lactoferrin, genetically modified