Animal Biopharming in New Zealand
Drivers, Scenarios and Practical Implications

Joanna Goven
Lesley Hunt
David Shamy
Jack A. Heinemann

Research Report no. 12

2008

Abbreviations

AI	Artificial Insemination
APEC	Asia Pacific Economic Cooperation
BSE	Bovine Spongiform Encephalopathy
CDER	Center for Drug Evaluation and Research
CHMP	EMEA Committee for Medicinal Products for Human Use
CJD	Creutzfeldt-Jakob disease
EMEA	European Medicines Agency
ERMA	Environmental Risk Management Authority
FDA	Food and Drug Administration
FRST	Foundation for Research, Science and Technology
FSANZ	Food Standards Australia and New Zealand
GRAS	Generally recognised as safe
HGT	Horizontal gene transfer
HSNO	Hazardous Substances and New Organisms
IBSC	Institutional Biological Safety Committee
IVF	In vitro fertilisation
MAF	Ministry of Agriculture and Forestry
MfE	Ministry for the Environment
MoRST	Ministry of Research, Science and Technology
NZTE	New Zealand Trade and Enterprise
OECD	Organization for Economic Cooperation and Development
RSNZ	Royal Society of New Zealand
TSE	Transmissible Spongiform Encephalopath

Executive Summary

The research presented here is premised on the assumption that in order to evaluate the risks and benefits, the desirability and ethics of a technology, we must know how it is likely to *interact with its context*. The research aims to identify the contexts relevant to the implementation of biopharming in New Zealand and to investigate whether and how the associated risks can be managed. It does this by eliciting relevant knowledge from people with experience and expertise in the identified contexts.

Animal biopharming is defined here as the farming of transgenic animals genetically modified to produce pharmaceutical compounds for use in humans. Plant biopharming is also under development. Biopharming is one of several methods that can be used to produce the class of drugs known as biopharmaceuticals. Animal biopharming research and development have focused primarily on dairy species.

The major drivers internationally for the development of animal biopharming are its potential to lower the costs of drug production, the greater ease of upscaling and downscaling production, an anticipated shortage of manufacturing capacity using other production methods, the potential to address some of the limitations of other production methods, and the desire to strengthen or evade patent restrictions. In New Zealand, major drivers include New Zealand's animal-health status, the strength of its dairy research and farm management, and a desire to use biopharming as a tool to move the economy away from commodity production and to enhance economic competitiveness. Biopharming research and development in New Zealand is currently focused on dairy cows.

Significant uncertainties remain regarding the potential benefits and hazards of biopharming. These include: cost-effectiveness in relation to competing platforms, unresolved technical problems, patent and regulatory issues, potential risks to human health, issues of gene spread, and animal-welfare concerns.

Factors to be considered when assessing the prospects, including the risks and benefits, of biopharming in New Zealand should include the nature of the biopharming enterprise (e.g., animals used, activities encompassed, and operational and ownership structure) as well as the risk management measures likely to be applied. Four scenarios have been developed for assessment based on these factors.

Factors relevant to risk assessment and management of biopharming emerging from the research encompass implications of the farm context for risk management as well as impacts of risk management on farm practice. The former include: impact of ownership structure, social and economic influences on implementation of controls, labour market, and the role of human error. The latter include: grazing practices, disposal of carcasses and waste, farm location, movements on and off the farm, and future land use.

Application of the research findings to the scenarios suggests that there are substantial obstacles in the way of animal biopharming being taken up by dairy farmers in New Zealand. Specialist integrated biopharm operations may not face the same obstacles, but may also not offer the prospective benefits that have driven research on biopharming in New Zealand. Application of the findings to risk assessment and risk management points to a need to include a wider range of knowledge in risk-assessment processes and to consider a wider range of factors in assessing risks and benefits and in developing risk-management protocols.

Chapter 1: Introduction

This report represents the findings of part of a research project[1] that asks: What do we need to know in order to make competent decisions about biopharming in New Zealand? The overall goal of the research on biopharming is to identify regulatory and governance needs and implications associated with biopharming and related technologies.

Animal biopharming

Animal biopharming is defined here as the farming of transgenic animals genetically modified to produce "humanised" pharmaceutical substances for use in humans. Biopharming is also known as "molecular farming". Examples of types of animal biopharming currently being researched include cows, sheep and goats modified to produce the substance in their milk and chickens modified to produce the substances in their eggs. Biopharming using plants is also under development.

No biopharmed products have yet reached the stage of commercial production. Many are in various stages of the research, development and approval process (see Table 1). In 2006, GTC Biotherapeutics/Genzyme Europe became the first company to be given permission to market a drug made in the body of a transgenic animal when it received marketing authorisation from the European Medicines Agency (EMEA) for Atryn®, a recombinant form of human antithrombin produced in transgenic goats (see Box 1).

Box 1. ATryn®

Atryn®, a recombinant form of human antithrombin produced in transgenic goats, became the first transgenic protein drug produced in an animal "bioreactor" to be approved for use as a human medicine in 2006 when it was approved by the EMEA for use in patients with congenital antithrombin deficiency undergoing surgery, to prevent deep-vein thrombosis and thromboembolism . EMEA's Committee for Medicinal Products for Human Use (CHMP) initially issued a negative opinion on Atryn® because of too few relevant clinical cases and insufficient studies looking for the development of antibodies. However, at the company's request, CHMP re-examined its opinion, agreed to include clinical cases eliminated earlier due to dosing inconsistencies, eventually recommending marketing authorisation. It suggested addressing the antibodies issue through close post-market monitoring by the company. Though some interpreted this decision as putting paid to fears that regulators would resist biopharm drugs, others saw EMEA approving an "infrequent use" drug in order to encourage development of processes to prepare recombinant pharmaceutical proteins, because "[t]hey want good proteins and they hope the method will work." (L. M. Houdebine quoted in Schmidt, 2006). ATryn® does not yet have USFDA approval but is in phase 3 trials for the same clinical use. ATryn® has also entered phase 2 trials in Europe for its use with disseminated intravascular coagulation (DIC) occurring in association with severe sepsis. (See www.gtc-bio.com and the EMeA document, 'Questions and answers on Atryn' at www.emea.eu.int).

---

[1] This research constitutes one part of the Constructive Conversations/Kōrero Whakaaetanga project; Foundation for Research, Science and Technology contract UOCX0221.

Table 1: Therapeutic proteins produced in transgenic animals currently in commercial development

Production Animal	Companies	Products	Developmental Stage
Cows	Bio Sidus	Human growth hormone	Preclinical
	GTC Biotherapeutics	Albumin	Preclinical
	Pharming	Collagen	Preclinical
	Pharming	Fibrinogen	Preclinical
	Pharming	Lactoferrin	Preclinical
Chickens	Avian Initiative	Recombinant proteins	
	AviGenics	Recombinant proteins	Clinical
	Origen Therapeutics	Human poly and monoclonal antibodies	Preclinical
	Viragen	Interferon alpha and single chain antibody	Preclinical
	Vivalis	Recombinant proteins	Preclinical
Fish	Ecoarray	Recombinant human factor VII	
Goats	Genzyme Transgenics and Genzyme	Antithrombin III	Phase 3
	GTC Biotherapeutics	Alpha-1 Antitrypsin	Phase 2 in EU
	GTC Biotherapeutics	ATryn	Approved in EU June 2, 2006 US: Phase 3
	GTC Biotherapeutics	CD137 (4-1BB) MAb (Antibody)	Preclinical
	GTC Biotherapeutics	Malaria Vaccine	Preclinical
	Merrimack and GTC Biotherapeutics	MM-093	Phase 2 RA
	Nexia Biotechnologies	Protexia (human butyrylcholinesterase) Spider Silk protein	Preclinical
	Pharmathene	Butyrylcholinesterase	Research
Pigs	Foulum Research Center	Alzheimer's model	Research
	North Carolina State University	Retinal pigmentosa Model	Research
	Progenetics	Factor –lX	Research
	Revivicor	Xenotransplantation (cartilage implants) Polyclonal antibodies	Research
	University of Missouri	Xenotransplantation	Research
Rabbits	BioProtein Technologies	Recombinant proteins	Research
	Pharming	Alpha-Glusidase	Phase 2, on hold
	Pharming	C1 Esterase Inhibitor	Phase 3 for HAE
	Pharming	Fibrinogen	Preclinical
	Pharming	Lactoferrin	Preclinical
	Therapeutic Human Proteins	Humanized polyclonal antibodies	Research

Sources: Kaye-Blake, Saunders, and Ferguson, 2007: 54-56; Keefer, Pommer and Robl, 2007; Echelard, Ziomek and Meade 2006: 38, Schmidt, 2006.

The pharmaceutical compounds produced through biopharming are a subset of the class of pharmaceuticals known as biopharmaceuticals. Biopharmaceuticals are medical drugs produced through biotechnology (rather than through chemical synthesis), by means other than direct extraction from a native (non-engineered) biological source (Walsh, 1998). They are typically manufactured through fermentation processes involving bacteria, yeasts, fungi or algae, or through cell cultures from insect, plant or animal cell systems (Elbehri, 2005; Dyck, 2003). Biopharming is thus one method, or "production platform", for the production of biopharmaceuticals.

Animal biopharming in New Zealand

New Zealand's strong agricultural experience and expertise, its freedom from animal diseases such as BSE, and the desire to move out of commodity markets have led to the identification of animal biopharming as a significant opportunity for New Zealand (MoRST, 2005: 67). According to MoRST's 2005 "futurewatch" report,

> [t]he production of high-value proteins (like pharmaceuticals), using plants or animals as bioreactors or "factories", is forecast to occur between 2007 and 2020. Biopharming using farm animals is forecast to occur before production in plants. (MoRST, 2005:11)

Animal biopharming research is occurring in New Zealand. Between 1999 and 2003, in Whakamaru, PPL Therapeutics developed a flock of transgenic sheep modified to produce recombinant human alpha-1-antitrypsin (hAAT). Since 1999, AgResearch has been producing transgenic cows modified to produce various human pharmaceutical proteins at their Hamilton-based research site, Ruakura. (See Chapter 2.)

Knowledge for assessing animal biopharming: structure of this report

The research presented here is premised on the assumption that in order to evaluate the risks and benefits, the desirability and ethics of a technology, we must know how it is likely to *interact with its context*. The research aims to identify the contexts relevant to the implementation of biopharming in New Zealand and to investigate whether and how the associated risks can be managed. It does this by eliciting relevant knowledge from people with experience and expertise in the identified contexts.

In order to carry out such a prospective assessment of a future development, it is necessary to understand the likely developmental trajectory of the technology. What shape is it likely to take in New Zealand if and when it goes beyond the field-testing stage to commercial production? This requires some understanding not only of what is technically possible, but also of the economic and social drivers behind the development of the technology. Chapter 2 presents a discussion of these drivers and the associated claims that are made about the future of biopharming.

Because much of biopharming's economic and medical promise is yet to be demonstrated, in Chapter 3 we present findings from the international literature

concerning the uncertainties and unknowns surrounding the potential benefits and harms of animal biopharming. As the Environmental Risk Management Authority (ERMA) must take into account both risks and benefits, an understanding of the uncertainties surrounding both is important for robust decision-making. It may also be of value to research funders, as decisions regarding the funding of research projects also take into account the future benefits claimed for the proposed research,.

In Chapter 4 we present possible scenarios for the commercialisation of animal biopharming in New Zealand, including the types of animals most likely to be used and the ownership and management conditions under which commercialisation is most likely to occur. These have been derived both from the literature and from data obtained from interviews with a range of key actors in New Zealand. These key actors came from the Ministry of Research, Science and Technology (MoRST), Ministry of Agriculture and Forestry (MAF), New Zealand Trade and Enterprise (NZTE), Biosecurity NZ, ERMA, AgResearch, Meat and Wool New Zealand, Fonterra[2] and an additional dairy cooperative, Vialactia, and LactoPharma.

In order to identify both the practices in the sector that may be impacted upon by the demands of biopharming and the sector practices that may represent risks in the context of biopharming, we carried out interviews with those directly involved in dairying (both caprine and bovine): a variety of dairy farmers supplying Fonterra, dairy-farmer representatives of Federated Farmers, and members of the NZ Dairy Goat Co-Operative and the Dairy Goat Breeders Association. We present the findings from these interviews in Chapter 5.

In Chapter 6 we conclude by discussing the implication of our findings for the prospects of biopharming in New Zealand, for its practical management and for its regulation.

---

[2] Fonterra Co-operative Group Ltd is a multinational dairy company, owned by 11,600 New Zealand dairy farmers. Fonterra shareholders make up over 95% of New Zealand dairy farmers (Fonterra 2006).

Chapter 2: Drivers and Prospects

This chapter presents the various claims, prospects and forces influencing the development of animal biopharming. The first part of this discussion highlights findings from the international science and technology literature, as well as "grey literature" (such as working papers, policy advice and commissioned research reports), on biopharming and related technologies. This is followed by a discussion of New Zealand-specific issues, based upon New Zealand literature and interviews with key actors. We end the chapter with a discussion of New Zealand-based biopharming research and development.

2.1. Generic drivers

2.1.1. Lowering production costs of biopharmaceuticals

The discussion of the merits of animal biopharming in the international literature is dominated by statements that it is expected to lower the costs of production of pharmaceuticals. It is claimed that biopharming will be a simpler, more efficient system with lower set-up costs that produces higher volumes of more stable proteins than traditional production methods. Current production methods (fermentation and cell cultures) are characterised as inefficient, expensive and time-consuming processes, while biopharming promises significantly lower infrastructure and operating costs (Echelard, Ziomek & Meade, 2006; Keefer, 2004; Kues and Niemann, 2004: 287; Rudolph, 1999; Laible & Wells, 2007: 112).

Dyck et al. (2003: 394-5) argue that transgenic technology offers the lowest-cost method for producing biopharmaceuticals: "[b]uilding a large-scale (10 000 l[itre] bioreactor) manufacturing facility for mammalian cells takes 3–5 years and costs US$250–500 million, whereas a transgenic farm with a single purification facility should not cost more than US$80 million, probably less." They posit that the cost of purification once the protein has been produced will be similar whatever the production system. They acknowledge, however, that it is difficult to carry out a direct comparison because there are so many unknowns such as "lack of data on protein yield, purification rates and production scale … [and] specific recombinant protein being produced".

2.1.2. Capacity shortage and flexible supply

Demand for recombinant pharmaceutical proteins is expected to grow, and manufacturing capacity is said to be a major constraint on future supply (Dyck et al., 2003: 394; Elbehri, 2005). The use of transgenic animals to produce biopharmaceuticals is presented as a way of addressing this predicted shortfall in manufacturing capacity (Houdebine, 2005; Dyck et al., 2003; ERMA, 2002: 44).

> [I]ndustry analysts expect an average of six or seven new large-molecule drugs to reach the market each year over the next several years. These monoclonal antibodies, which require a large production capacity, are expected to make up about a third of all new therapeutics … [C]urrent cell culture facilities are unlikely to meet the expected demand. (Ginsberg, Bhatia, & McMinn, 2002)

According to Elbehri (2005: 19, citing Fernandez, Crawford, & Hefferan [2002]),

> each newly approved monoclonal antibody requires 100,000 kg of production annually requiring new fermentation capacity to be built. To meet the expected demand for new drug production, more than three times the current production capacity may be required. It is estimated that 20–50% of potential therapeutics industry wide could be delayed due to the lack of manufacturing capacity.

This focus on capacity was sparked by the case of Enbrel, a drug produced by Immunex that treats rheumatoid arthritis. Enbrel is produced in 10,000 litre bioreactors of cultured Chinese hamster cells. It was approved by FDA in 1998 and experienced a supply shortage by 2001 (Thiel, 2004; Elbehri, 2005). By 2002 there was a waiting list of 13,000 patients, and Immunex began rationing it.[3]

An important dimension of biopharming's predicted cost-effectiveness is the ability to scale production up or down quickly (in response to demand) simply by increasing or decreasing the number of animals required and/or their lactation. This is contrasted to the need, when using current fermentation or cell-culture methods, to build expensive new facilities in order to increase production (Laible & Wells, 2007: 112; Keefer et al., 2007: 4, 6; Dove, 2000; Rudolph 1999; Bialy, 1991).

2.1.3. Opportunities for patent-enhancing and patent-busting

Rather than producing new medicines, biopharming may be seen instead as a way to reinforce or undermine patents on existing medicines. A number of biopharmaceuticals are due to come off-patent in the near future. Biopharming may enable a company to acquire a new patent for the same drug on the basis of its different production method. Conversely, "the expiration of the patents for many first generation biopharmaceuticals, predominantly produced in cultured mammalian cells, provides additional opportunities for the production of 'biosimilars', essentially equivalent recombinant proteins of previously approved pharmaceuticals[,] from transgenic animals" (Laible & Wells, 2007: 113). Biopharming may also enable companies to "bust" existing patents by developing a new process to produce a substance whose patent is associated with another method of production. These prospects are heavily dependent on regulatory and patent-agency decisions.

---

[3] Others question whether this case points to a more general shortage of capacity, for example, Thiel (2004). See Chapter 3.

2.1.4. Potential for new and better drugs

Some argue that another driver for animal biopharming is its potential to produce biopharmaceuticals that cannot be produced in other ways (Keefer et al., 2007; Thiel, 2004; Dove, 2000). Dyck et al. (2003: 395) note problems with other production platforms (bacteria, yeast, and insect, metazoan and mammalian cells) and suggest that transgenic animals (and plants) may avoid these problems, thus presumably enabling successful production of drugs that could not (or would not) otherwise be produced.

It is also argued by some that animals have quality advantages over plants or micro-organisms as a production platform for biopharmaceuticals. "[T]ransgenic animals are well equipped to perform all of the complex post-translational modifications necessary to render some proteins biologically active" (Dyck et al., 2003: 395). Because of their greater similarity to humans, animals generate post-translational modifications that, it is argued, are likely to result in more "human" proteins than those produced through transgenic plants or micro-organisms (Laible & Wells, 2007: 112; FRST, 2005, Bialy, 1991; ERMA, 2002: 44).[4] This could reduce the allergenicity or immunogenicity of the drug, or enhance its effectiveness. On the other hand, the fact that biopharm animals are non-human is said to reduce the risk of contamination from and hence, transmission of, human pathogens such as human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) or Creutzfeldt-Jakob disease (CJD) compared to human cell lines (Laible & Wells, 2007; Keefer et al., 2007).

2.1.5. Economic advantages of dairy species

The general consensus is that milk-producing mammals are the best candidates for biopharming. Other bodily fluids and tissues can also be used for biopharming (MoRST, 2005, p.69); however, compared to other candidate fluids and tissues, milk is produced in large volumes, relatively high concentrations of recombinant proteins can be produced in milk, and milk is easily collected (Laible & Wells, 2007; Houdebine, 1995; Bialy, 1991). Milk is regarded as a less complex fluid than blood, and so production of the expressed proteins is simpler and less expensive. Milk products are also regarded as being less likely to produce adverse reactions in humans (Thomson and McWhir, 2004: 234) and to be safer than those produced from human fluids (Keefer, 2004: 9). For that reason, "a great deal of effort has been made to produce transgenic bioreactors with the traditional 'dairy' species, such as sheep, goats and cows" (Dyck et al., 2003: 395).

According to Baguisi et al. (1999) and Dove (2000: 1048), goats are well-suited for biopharming as they have a quicker breeding cycle than cattle and produce more milk than sheep. Female goats (does) mature to a reproductive age more quickly, have a shorter gestation period (six months) and are fertile again six months after birth (Redherring, 2006). Overall they have a generation time of 18 months compared with 3 months for mice and three years for cows (GTC Therapeutics, n.d.(1)). Hence herds of

---

[4] On post-translational modification, see Box 2, section 3.2.1.

biopharm does would naturally lactate sooner than cows and could thus potentially be scaled up more quickly.

The major advantage of cows for biopharming is the volume of milk they produce. A cow's annual production of milk can exceed 10,000 litres (Bialy, 1991: 786-8).

2.2. New Zealand drivers

Many of the arguments already outlined above are also present in discussions of animal biopharming in New Zealand, but while the international literature has highlighted the prospects for the biotechnology and pharmaceutical industries, the discussion in New Zealand has placed considerable emphasis on returns to farmers, the composition of exports, and a related transformation of the New Zealand economy. David Powell of NZTE argued:

> The key benefit of bio-pharming is that the financial returns to growers and farmers are many times higher than those in conventional farming… Bio-pharming is also of interest because the high value pharmaceutical products produced will escape the current food-based quotas that many of our exports are penalised or prohibited under, further expanding marketing possibilities. (Powell 2001)

According to Beckman and Goldberg (2003) in a report commissioned by Industry New Zealand, "the use of transgenic animals to generate large amounts of human-protein-based drugs is a natural fit for New Zealand", while Paul Pickering of Virionyx Corporation mainted that:

> With its disease-free status, a long history of efficient and innovative farm management practices, as well as top quality biomedical research, New Zealand has huge potential to claim its place as the world's natural home for the development and commercialisation of novel animal and plant derived human therapeutics. (P. Pickering, quoted in Powell 2001)

2.2.1. Wealth generation and economic competitiveness

As noted above, it is argued animal biopharming will benefit the farming industry in New Zealand. Scientists and business managers we interviewed emphasised that it would provide farmers with an option for producing more valuable products. By producing pharmaceuticals in the milk of a dairy herd, biopharming appears to meet the oft-cited need for New Zealand's agricultural sector to shift from the production of commodity goods to higher-value-added goods for export.

The development of biopharming is seen to be an important strategy to increase New Zealand's economic competitiveness. New Zealand has traditionally relied on efficient

production methods to produce large quantities of commodities that are price-competitive on overseas markets. It is argued that as other countries, particularly in Asia and South America, become more efficient commodity producers, New Zealand's primary-production sector will become considerably less profitable. Applying biotechnology to the agricultural sector is seen as one solution to this problem. FRST notes in relation to its funding of AgResearch's biopharming research that the "long term aim of the research is to maintain and enhance the competitive position of New Zealand's agricultural sector in the global market …" (FRST, n.d.).

NZTE argues for a focus on the development of higher-value products from the primary production sector and that the highest revenues from biotechnology for the primary production sector will be derived from non-food health applications (NZTE, 2005). Biopharming is particularly attractive as it promises to give the sector access to the high profit levels of the pharmaceutical industry. It is recognised that the attractiveness of biopharming to investors lies in its potential for reduced costs of production. MoRST has claimed that specialist drugs may be produced through animal biopharming at one thousandth the current cost of production (MoRST, 2005: 68).

2.2.2. The advantage of disease-free status

New Zealand's animal-health status is seen as a major competitive advantage. New Zealand is free from Foot and Mouth Disease and from scrapie and the related prion diseases, Transmissible Spongiform Encephalopathies (TSEs). In fact, Beckman and Goldberg (2003: 10) make the claim that "the country can boast the 'cleanest' animals on the earth". This point is prominent throughout the New Zealand literature (e.g., Laible & Wells, 2007; MoRST, 2006; L.E.K., 2006). Furthermore, New Zealand is regarded as having strict regulatory processes which maintain this 'clean' disease-free status.

Kues and Neimann (2004: 288) note that the FDA's general guidelines require close control and monitoring of animal health and performance of the transgenic animal over several generations. They suggest that biopharming should be conducted using animals from disease-free countries to make this process easier. It is notable that the one drug/medicine from a biopharm animal that has been approved for use, GTC Biotherapeutic's ATryn®, is made from milk of a transgenic goat herd that was established through the importation of goats from New Zealand certified as scrapie-free by the USDA[5].

2.2.3. Strong dairy and research sector

Other attributes of New Zealand's farming sector also contribute to the belief that New Zealand has an advantageous position from which to develop animal biopharming: namely, expertise and experience in (dairy) farm management and a strong dairy research sector. Beckman and Goldberg (2003) claim that "dairy farming and animal husbandry are marvelously developed businesses in New Zealand", while MoRST (2005: 67) argues that New Zealand expertise in farm management, animal husbandry systems, and veterinary care may also encourage foreign companies to invest in animal biopharming

---

[5] From the GTC Biotherapeutics website: www.gtc-bio.com/science/howitworks.html

15

here. New Zealand has had strong backing both privately and by government for basic research on cattle, which may be helpful for the development of animal biopharming (Beckman & Goldberg, 2003:10)

2.3. Biopharming research and development in New Zealand

Two biopharming research and development projects have reached the stage of field trials in New Zealand. Between 1999 and 2003, Scotland-based PPL Therapeutics developed a flock of transgenic sheep engineered to express recombinant human alpha-1-antitrypsin [rhAAT] in their milk. The declared intention was to use rhAAT to develop treatments for lung ailments. The flock was located at Whakamaru, near Rotorua.

In 2003, PPL announced that it was putting this research "on hold", because its development partner, the pharmaceutical company Bayer, had suspended its development of the treatment.[6] It is not clear whether Bayer's suspension resulted from lack of effectiveness of the treatment or a change in the economics of that market (Hunt et al., 2003: 8-9). The companies, in a joint statement, reported that the "resources required to move the project forward, combined with the decision not to build a commercial purification facility because of the financial risk, have led the companies to the decision to place the project on hold" (Associated Press, 2003).

At the time the research was suspended, there were approximately 4000 rhAAT-producing transgenic sheep in the flock (ERMA 2003). ERMA responded by increasing the frequency of inspections of the facility from three-monthly to weekly. PPL was reported to be "undertaking a managed reduction of their flock, particularly through reducing the number of older sheep … in accordance with controls on the approval" (ERMA 2003). The facility was closed in March 2004 and the land sold to Whakamaru Farms Limited, which is described (on the Innovation Waikato website) as "a biotech company which does large animal work on a contract or joint venture basis." In 2004 the site was reported as being used for contract grazing of dairy cows (GE Free NZ, 2004).

ERMA's 1999 approval stipulated that "[i]n the event that operations cease all sheep in the containment facilities shall be destroyed and all biological material derived from transgenic sheep be incinerated, and Ngati Raukawa shall be invited to undertake a Whakanoa or ritual cleansing ceremony." ERMA had not made stipulations regarding future uses, or monitoring, of the land on which the trial took place, which led to an unsuccessful legal challenge being taken against ERMA that sought the imposition of ongoing controls.

The second biopharming research and development project is ongoing at AgResearch. In 2001, ERMA approved an application from AgResearch (GMF98009) to produce cattle genetically modified to express recombinant human myelin basic protein in their milk. In

---

[6] See "PPL Therapeutics Limited Update" on the ERMA website, http://www.ermanz.govt.nz/news-events/archives/media-releases/2003/mr-20030717.html

2002, ERMA approved a further application (GMD02028) "to develop transgenic cattle that can express functional therapeutic foreign proteins in their milk and to develop transgenic cattle to study gene function and genetic performance" (ERMA 2002). The proteins were not specified; the application sought a generic approval. While application was made under the "development" category, it was intended to encompass a herd of transgenic cows held in outdoor containment.

AgResearch has since applied to ERMA for a number of amendments of the 2002 decision. The original ERMA decision had excluded use of: all viral sequences other than SV40 and the EBV origin of replication; from the vector insert, all bacterial sequences other than reporter gene and marker genes, and their associated promoters, and multiple cloning sites derived from non-pathogenic strains of *E. coli* bacteria; known animal (as well as human) viral receptors; antibiotic resistance markers conferring resistance to antibiotics of clinical significance in veterinary or human medicine; and genes associated with the development of transmissible spongiform encephalopathies (prion diseases) (ERMA2002). In 2005 AgResearch was given approval to use a selectable marker gene coding for resistance to puromycin (an antibiotic). In 2005, they were also granted approval to use imported sperm and embryos from transgenic animals to develop the herd, while the original approval had been premised on development of transgenic embryos in New Zealand though cell culture, transfection, selection of stable cell clones and nuclear transfer. In 2007, AgResearch applied under GMD02028 to be permitted to use two genetic sequences of viral origin (ERMA 2007a); at the time of writing, there had not yet been a decision on this application.

The aspects of this research funded by FRST under the title 'Transgenic cattle producing valuable proteins' are described as aiming "to build, through cloned-transgenic cattle, a new biotechnology based pharmaceutical/nutraceutical industry in NZ" (FRST 2005a). AgResearch reported that it has "entered into an agreement with the Dutch company Pharming to establish a small number of cattle for the production of human lactoferrin" (FRST 2006c). According to an industry report, under the agreement AgResearch's responsibilities include:

> production of rhLF [recombinant human lactoferrin] and purification, as well as providing research capabilities for product development. AgResearch will also fund the initial production of rhLF and support the commercialisation of the ingredient in the South Pacific and Asia. (Taylor, 2005)

In return for granting AgResearch a research license to its proprietary technology for the production of recombinant proteins, Pharming:

> will have the first right to review new products arising out of AgResearch's protein discovery and R&D projects. The commercial rights of Pharming will cover recombinant bovine and human proteins produced using its proprietary technology. (Taylor, 2005)

AgResearch had also established a commercial relationship with PPL Therapeutics before its demise, which it described as securing for AgResearch "the commercial freedom to operate for future NZ biotechnology enterprises in this highly lucrative market" (FRST, 2005a).

In late 2007, AgResearch announced that it would apply to ERMA in April 2008 to extend and expand its biopharming research and development. It will seek permission to hold biopharm cattle in containment anywhere in New Zealand, to produce nutriceutical and pharmaceutical commercial products from biopharm milk, and to extend its biopharm activity to include goats (NZPA, 2007). According to General Manager Jimmy Suttie:

> The approvals AgResearch will be seeking in 2008 are for a range of activities, from pure scientific research, to maintaining transgenic animals in containment for the production of speciality milks or milk products (e.g. lactoferrin), and the production of biopharmaceutical (medical) proteins. Current commercial projects are in both the medical food area and in biopharmaceuticals. (Suttie, 2007)

Chapter 3: Uncertainties and Unknowns

The potential benefits and harms of animal biopharming are characterised by significant uncertainties and unknowns. The techniques used for the development of transgenic animals are characterised by technical and ethical difficulties (Keefer et al., 2007; Laible & Wells, 2007). The scientific research that may be necessary for a competent evaluation of the risks of commercial production is underdeveloped. Market demand as well as the rules and regulations for the development and use of biopharm products are yet to be tested. These uncertainties are reflected in the lack of investor interest noted by Ledford (2006: 16): "Venture capitalists have largely shied away from the technology, and bigger pharmaceutical companies have not embraced it either."

This chapter covers the uncertainties associated with the purported benefits and hazards of biopharming. When risk assessments are carried out, potential hazards that are identified are typically weighed against potential benefits. For this process to be robust, the uncertainties around the potential benefits, as well as the potential hazards, must be evaluated.

3.1. Uncertainties regarding benefits

3.1.1. Capacity and competing platforms

It was noted in Chapter 2 that one of the major economic arguments for biopharming is a purported lack of adequate capacity to meet the potential future demand for biopharmaceuticals. However, in a review of these arguments in the journal *Nature Biotechnology*, Thiel (2004) suggests that the biopharmaceutical manufacturing bubble may have burst. He argues that the shortage of Enbrel was an aberration rather than indicative of the situation within the industry as a whole, even suggesting that there may now in fact be some excess manufacturing capacity worldwide.

Future capacity needs will also be affected by changes to biomanufacturing technologies. Improvements have been made in cell-line yields, and disposable bioreactors have been developed, introducing more flexibility into lab-based production.

> Traditional cell-line manufacturing, whether in microbial or mammalian hosts, is advancing in ways that could dramatically change how facilities are built and operated. Potentially revolutionary but commercially unproven transgenic production platforms, meanwhile, may become a tougher sell to industry … [R]apid advancements in cell-based manufacturing technologies and strategies … pose considerable threats to companies hoping to do contract manufacturing in transgenic plants or animals. (Thiel, 2004: 1365, 1368)

A second major economic argument in support of biopharming claims that it will lower production costs. But according to Thiel (2004: 1369-70), the cost advantages of biopharming over traditional methods are now less clear than they appeared at the time of the Enbrel supply crisis.

> [B]iotech companies looking at options for commercial production of biologics see available capacity and a future of increasing efficiency in traditional cell-line production …. [T]here is little immediate pressure for companies to move to alternative platforms that are as yet commercially unproven. (ibid.: 1370)

Whether any of this will change in response to the ATryn® approval is not yet clear. Thiel quotes an industry participant who argues that:

> [T]he cost advantage boasted by transgenics will dwindle as traditional cell culture manufacturing becomes more productive with new, more efficient cell lines … There are a lot of hidden costs in producing transgenics that I'm not sure anyone really understands, and I'm not sure they will until they do it at scale. (Thiel, 2004: 1371)

Another industry participant doubts that there will be significant cost savings once containment costs, the need for purification facilities, and the possibility that additional purification steps may be required are figured in (Thiel, 2004: 1371).

Saint-Jore-Dupas et al. (2007) suggest that recent advances in the manipulation of plant glycosylation[7] mean that what was regarded as a handicap in the use of plants as expression systems for the production of recombinant pharmaceutical proteins may turn into an advantage, as researchers have been able to humanise the plant-specific glycosylation processes. They see this as a way of overcoming some of the difficulties associated with the use of mammalian cells and animal production systems, particularly the potential for the transmission of viruses and prion diseases.[8]

It is perhaps worth noting that Texas-based firm Agennix claims that it can produce recombinant human lactoferrin through microbial fermentation processes at costs similar to those expected to be incurred by Ventria Bioscience's plant biopharming platform (rice engineered with the genes for the production of human lactoferrin) (Wisner, 2005: 16, 27). As noted above, in 2005 AgResearch signed a deal with Pharming NV to produce recombinant human lactoferrin in cows. This suggests the possibility that biopharming's cost advantages may be whittled away by competing platforms.

---

[7] "[M]ore than half of the human proteins are glycosylated and their function frequently depends on particular glycoforms (glycans) which affect their plasma half-life, tissue targeting and/or biological activity. Similarly, more than one-third of approved biopharmaceuticals are glyco-proteins and both their function and efficiency are affected by the presence and composition of their *N*-glycans" (Saint-Jore-Dupas et al., 2007: 317). (On glycosylation see Box 2, section 3.2.1.)

[8] Others, however, argue that "humanised" plants may pose their own risks in this regard, as "plant viruses passing through humanized plants might have altered infectious ranges for both plants and animals" (Heinemann, 2007:45).

3.1.2. Scalability and unresolved technical problems

While the ability to upscale or downscale production rapidly and economically is seen as a major economic advantage of biopharming, it is not yet clear how well this applies to animal (as opposed to plant) biopharming. Production of the animal does not of course result in immediate production of the product. The candidate dairy species take varying but substantial times to reach first lactation (see Chapter 4).

Current technology for generating biopharm animals is beset by problems that could affect the economic viability of a commercial operation.[9] (The associated animal welfare concerns are discussed in section 3.2.4.) Live animals produced through transgenesis or as offspring of transgenic animals may be nontransgenic, 'silent' (not expressing the transgene) or male (Keefer et al., 2007: 2) . While cloning has been used to reduce the number of generations needed to produce a transgenic herd, this method is characterised by low survival rates and health problems (Dove, 2000: 1046; Laible & Wells, 2007).

The low survival rate of embryos and animals generated by biopharm animal production technologies is regarded as one of the problems that must be addressed if biopharming is to be a commercially viable strategy for the future (Clark and Whitelaw, 2003: 828). According to Fiester (2005:331), with reference to animal cloning in general, only 1-2% of transferred embryos result in live offspring. Laible and Wells (2007: 106) note with reference to cloned cattle that in addition to these low rates of live births, a significant proportion of the resulting animals die before weaning,. Studies of other animal species similarly show high rates of early death and physical abnormalities (Fiester 2005:331-332).

In relation to the pronuclear microinjection technique used in the creation of transgenic animals, Dyck et al. (2003) maintain:

> [T]he unpredictability of transgene behaviour is problematic and has lead [*sic*] to the search for alternative gene transfer strategies. However, none of the alternatives to date has done so without burdening the transgenic animal production system with additional pitfalls. Furthermore, for reproductively efficient species, including mice, rabbits and pigs, this inefficiency is less prohibitive than for less prolific species, such as goats, sheep and cattle. (Dyck et al., 2003: 397)

With pronuclear microinjection, the transgene may incorporate later in the process than desired, producing a mosaic animal in which some cells contain the transgene and some do not (Keefer et al., 2007).

---

[9] The process for establishing a transgenic herd of animals uses both transgenesis and cloning. Usually clones are made from donor cells taken from the transgenic female founder animals (Dove, 2000: 1046; GTC Biotherapeutics, n.d.).

3.1.3. Purification

In 2003, Dyck et al. identified purification as a potential obstacle to animal biopharming's commercialisation:

> [T]he raw potential for producing valuable proteins with transgenic animals seems apparent. However, the purification of these proteins from their source, whether milk, eggs or semen, is still a hurdle to be overcome and creates, often undefined, regulatory issues. (Dyck et al., 2003: 396; see also Gavin, 2001)

In 2004, purification was seen as the bottleneck for all biologics, whether products of transgenic animals or traditional cell-line manufacturing (Thiel, 2004, 1371). Purification of a recombinant protein in commercially viable amounts from the milk of transgenic animals is a critical but complicated process with a number of unknowns (Goldman, 2003: 5).

3.1.4. Patent issues

While research using transgenic animals to produce proteins is relatively unconstrained, the situation is different for commercial production. Many of the processes and substances involved in commercial biopharming, including processes used in the production of transgenic animals, protein characterisation, and the production of pharmaceuticals themselves, have already been patented. Negotiating through this patent thicket could be time-consuming and expensive. (Dyck, 2003: 397).

As noted above, biopharming is seen by some as a profitable way to avoid or extend patents by producing existing drugs in new ways. However, the future for these so-called biosimilars (or "biogenerics") is still unclear. In an interview reported in *Nature Biotechnology*, Pharming's chief business officer emphasised that "regulators respond more favorably to transgenic proteins developed for unmet needs" (Schmidt, 2006), that is, new drugs, and particularly those developed for "orphan"[10] diseases. It is not yet clear whether regulators will require biosimilar drugs produced through biopharming to go through the same approval process as new drugs (Somers, 2007; RSNZ News, 2006(1); FDA, n.d.,a), thus eroding their profitability and attractiveness to drug producers.

These potential regulatory requirements are related to the nature of biopharmaceuticals, as opposed to drugs produced through chemical synthesis.

> [Biopharmaceutical proteins] are in general 100-1,000 times larger than small molecules [produced through chemical synthesis], they can't be fully characterized physiochemically by current analytical methods, which are often insufficiently sensitive, and their mode of action can confound biological characterization *in vitro*. Unlike the chemical processes used to synthesize the

---

[10] This terminology refers to rare diseases whose low prevalence makes them financially unattractive as research and development targets for pharmaceutical companies under normal circumstances.

small molecules, therapeutic proteins are manufactured in living cells, which are very sensitive to culture conditions.

Even under the most stringently controlled culture conditions, proteins show a high degree of heterogeneity (e.g., in glycosylation or in folding). Often, modifications occur as a result of abnormal processing because the recombinant proteins are unnatural products for the cellular expression system used. Extraction and purification involves [*sic*] many steps that can also introduce protein modifications that influence biological activity or clinical properties….Production normally involves many hundreds of control steps, which involve numerous in-house standards. This complexity is the basis of the claim in pharmaceutical biotechnology that process is the product….

A major problem for generics manufacturers is the lack of access to production details, in-house controls and material from different stages of production … at the innovator company. (Schellekens, 2004: 1357, 1358)

This is discussed further in the following section.

3.1.5. Regulatory uncertainty

According to Laible & Wells (2007: 111), "one of the [chief contributors] to the slow commercial start of transgenic animal products, aside from uncertainties surrounding consumer acceptance, is the current status of the regulatory frameworks". Concerns that arise for regulatory authorities include: drug safety issues, protection of the food chain, environmental impacts and animal welfare (Keefer et al., 2007: 7).

Drug safety issues include, for example, the possibility of passing on viral or prion infection and the possibility of triggering immune reactions. Amy Rosenberg of US FDA notes:

We would really need assurance that the animals aren't infected with any kind of prion disease. And each product poses its own unique risk—for instance, recombinant versions of endogenous proteins might pose immunogenicity risks that you might not encounter if the protein doesn't have a human counterpart. (quoted in Schmidt, 2006)

The fear of transmission of a prion disease (TSE) could be seen as impacting in two ways on the possibilities for biopharming in New Zealand – the first being the encouragement of the use of New Zealand sourced animals both here and overseas, the second being the discouragement of *any* use of cloven-hoofed animals such as sheep, cattle or goats or animal sourced tissues (cell cultures) to produce pharmaceuticals. The former would make New Zealand a source of disease-free animals which could be cloned to further reduce the risk, as is under consideration by the FDA (see White, 2005: 2-3). The latter would obviously have a negative impact on New Zealand's aspirations for a biopharmaceutical industry based on this capability. (This latter possibility was suggested to us by one of the scientists we interviewed; it was his view of the direction FDA was likely to take.)

According to Schellekens (2004: 1357-8):

> [P]erhaps the most important difference between small-molecule drugs and recombinant proteins is immunogenicity. Protein biopharmaceuticals induce antibodies and these antibodies may have serious clinical consequences.

Others have pointed out, however, that animal biopharming may not differ on these points from other platforms already in use, such as mammalian cell lines. Some FDA officials agree; one has been quoted as saying "I don't see any show stoppers for these kinds of products" (quoted in Schmidt, 2006).

The use of animal biopharming to produce biosimilars raises its own regulatory issues. Regulatory agencies face particular challenges when it comes to evaluating biosimilars, however they are produced.

> For regulatory agencies, a key question is how similar the physiochemical characteristics of the biosimilar and its patented counterpart need to be to qualify for the biosimilar route of marketing authorization. Even if the biosimilar product has the same gene sequence, vector, host cell line, culture conditions and purification methods as the innovative protein, it can still differ substantially in its biological and clinical properties. (Schellekins, 2004: 1358)

If this is true of biosimilars using the same production methods as the original biopharmaceutical, it will presumably apply *a fortiori* to those using a different production platform.

While the regulation of biosimilars is still under debate in the U.S. (Somers, 2007), the European Medicines Agency (EMEA) has produced guidelines for evaluating biosimilars (Hirschler, 2005). According to Schellekens (2004: 1357), under these guidelines, the biosimilars developer may not have to repeat all of the toxicity studies undertaken by the developer of the innovator product. To make major costs savings, however, it would be necessary to avoid repeating expensive clinical studies of efficacy. The EMEA guidelines require that the biosimilar be shown to be similar to the original product "for every indication" (*ibid.*). Schellekens notes:

> [S]ome of the efficacy studies for a biosimilar may need even more patients than the original studies because efficacy must be shown to be equivalent to the original protein. In addition, a generic manufacturer will have to generate additional data on physiochemical comparability, bioequivalence in animals and patients, and clinical data on immunogenicity. Thus, the biosimilar route may turn out to be of even greater complexity than that for a new protein therapeutic. (2004: 1359)

This suggests that blanket approval of animal biopharming as a process for the production of biosimilars may be unlikely.

One could question whether animal biopharming is feasible or desirable without extensive and expensive monitoring of the processes and conditions of production. Keefer et al. warn that "[t]he stringent health surveillance for potential health hazards in the production herd must be factored into the economic equation" (2007: 6). Not only must the purity of the pharmaceutical substance be ensured, but also the surrounding environment and the food supply must be protected from inadvertent introduction of pharmaceutical substances. It is not yet clear what impact this will have on the profitability of biopharming.

Further, the stringency of regulations may depend on whether the product being produced is marketed as a nutriceutical or a pharmaceutical. A nutriceutical is a food or food extract that is claimed to have medicinal or health benefits beyond basic nutrition, but is not classed as a drug. While such products may be able to avoid some of the regulatory requirements described above, it is not clear whether biopharming will be a cost-effective way to produce nutriceuticals. (See the discussion of lactoferrin in Kaye-Blake et al. [2007: 32-33].)

3.1.6. Who benefits?

There is considerable uncertainty around who is likely to benefit from biopharming, should it prove feasible and profitable.

For example, even if animal biopharming does prove to be a cheaper method for producing drugs, it does not necessarily follow that either patients or health services will benefit from lower drug costs. As Ma et al. (2005: 594) note: "'Cost of goods' has relatively little impact on the market price of new pharmaceuticals." Moreover, as suggested above, complex biopharmaceutical production processes may mean that cheaper knock-off drugs will be harder to produce, in which case it is possible to question whether the cheaper production methods of animal biopharming will necessarily lead to a greater availability or affordability of drugs for patients (Herrera, 2004). (Indeed, MoRST [2005:90] has suggested that pharmaceutical companies will focus on biopharming as a novel way of producing purer drugs that are harder to copy.)

Whether or not farmers will benefit from biopharming depends on a number of factors, including ownership or management arrangements, the impact of patents, and the degree of market power. In a report on the potential benefits and hazards for farmers and rural communities of plant biopharming, Wisner (2005) asserts that the claims made for pharmaceutical crops are inflated and that farmers will not be the beneficiaries. This is because farmers will not be in a position of strength to negotiate with pharmaceutical companies, and international competition will be such that farmers will not be able to make reasonable profits. The amount of acreage required to grow pharmaceutical crops will be so small compared with commodity crops that it will not affect most farmers anyway. He also did not see rural communities as gaining any benefits unless the related research was carried out in nearby universities and processing companies were located in the community. Wisner argues that pharmaceutical companies are likely to be the prime beneficiaries of plant biopharming.

Other issues to consider include the impacts on non-biopharm farmers and the possibility that co-existence with biopharm dairying may impact upon markets for non-biopharm conventional (and organic) dairy products. A preliminary economic analysis of the hypothetical commercial production of recombinant human lactoferrin (rhLF) in biopharm cows, carried out for this research programme, concluded:

> [S]ocial 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. (Kaye-Blake et al., 2007: 33)

3.2. Uncertainties regarding hazards

3.2.1. Health risks for humans from biopharm drugs

Amy Rosenberg, supervisory medical officer with the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research, places health risks from biopharm drugs into four categories: infection; allergenic responses; immunogenic responses; and "autoimmune reactions arising should transgenic proteins break tolerance to their endogenous, self-protein counterparts" (quoted in Schmidt, 2006).

Many have focused on the potential for drugs made with animal bioreactors to transmit disease. For example, Laible & Wells (2007: 113) state, "The main safety concerns for pharmaceutical proteins derived from transgenic animals are the contamination with infectious agents (in particular prions in cattle)." Prions are associated with Transmissible Spongioform Encephalopathies (TSEs), including BSE, variant Creutzfeldt-Jakob disease (vCJD) and scrapie. Processes for reducing the risk of prion diseases include the use of scrapie-free animals in the production of any products which could potentially transmit a TSE (White, 2005). As New Zealand and Australia are the only countries to be declared scrapie-free, this has obvious importance for New Zealand.

Prion proteins are protein aggregates that transmit a trait as if they were based on DNA (Campbell, 1998; Keyes, 1999; Weld, 2002). Some suggest that prion diseases could develop in the community through the use of genetically modified animals (Weaver, 2003: 25). This may happen if a prion is consumed through drinking the cow's milk (U.S National Research Council, 2002: 52). In the case of prions, the infection requires a highly similar protein to be part of the normal proteins in the exposed recipient. However, all proteins have the capacity to aggregate, even if all do not become infectious, and there remains the formal possibility that other deleterious effects arise from aggregation itself (e.g., Bucciantini, 2002). Transgenic animals may be more prone

to deposit protein aggregates composed of the recombinant protein because the protein is usually produced at unnaturally high concentrations in recombinant animals or because the cell physiology of the recombinant animal is outside of the biophysical conditions of the source species (Tartaglia, 2007).

Other hazards may be linked to the techniques used to produce transgenic animals. The use of the transgenesis technique of pronuclear microinjection can produce unpredictable changes in the resulting organism (Dyck, 2003: 397; Keefer et al., 2007: 2). For example, the milk produced by transgenic animals can have quite different characteristics from 'normal' milk. Laible & Wells, reporting on their attempts to change the casein content of bovine milk, note:

> Interestingly, the simple increase in gene dosage for two milk proteins resulted in complex changes including effects on the production of some other milk proteins, mineral balance and physical appearance. Although not necessarily unexpected, complex changes as a result of genetic modification are difficult to predict and can only be assessed in the transgenic animals once generated. (2007: 115)

This example illustrates one of the important problems associated with the production of proteins from transgenic animals: how can non-obvious unanticipated changes be identified in transgenic animals if one does not know what to look for? Elbehri (2005: 20) and Saint-Jore-Dupas et al. (2007) perceive this to be an advantage of using plant, rather than animal, bioreactors, on the grounds that unexpected pathological changes are more likely to be transmissible to humans from animals than from plants.[11]

In terms of its impact on health risks, the glycosylation process is discussed as both an advantage and a risk of animal biopharming. Laible & Wells (2007: 113) point out that immune responses can occur "due to slightly varied glycosylation patterns compared with the native human equivalent". This is a concern for regulators because "although the transgene may code for a human protein, modifications may be made to the protein during its production in the transgenic animals" (Keefer et al, 2007: 7). (See Box 2 below.) Not only that, but "altered glycosylation patterns can affect the amount of time before a protein is cleared from a patient's system which can affect treatment protocols" (ibid.). Schmidt (2006) points out that it was concern about these two problems that held up EMEA's approval process for ATryn®.

However, as noted above, others maintain that animal biopharming may not differ in this regard from other techniques already in use for the production of biopharmaceuticals, such as those using mammalian cell lines (e.g., Laible & Wells, 2007: 113).

---

[11] But see Heinemann (2007).

Box 2: Post-translational modifications and glycoproteins

The primary structure of proteins is the linear order of amino acids which compose them. Proteins are more than just a sequence of amino acids, however. They may also be modified by addition of different kinds of molecules to various amino acids. This is relevant to risk assessment because the modifications can alter protein structure and function, as well as change the potential for the protein to be a toxin or allergen.

There are many forms of post-translational modifications. Most are the addition of molecules, but some modifications result from removing amino acids or re-folding a protein into an alternative three dimensional structure. The range of potential post-translational modifications varies by species, tissue and stage of development (Gomord et al., 2005).

Modification has medical and food relevance because, for example, proteins modified in plants can be immunogenic in humans (e.g. Prescott et al., 2005) and may cause cross-reactivity to similar epitopes (i.e., immunogenic regions) that occur in proteins from animal sources. The same protein can exist in hundreds to thousands of different isoforms in the same cell at the same time, but each form may not exist at the same concentration. Thus, detecting different forms can be very difficult.

More than 300 different types of chemical modifications are known, and are distributed among the following types: ubiquitination, halogenation, phosphorylation, farnesylation, glycosylation, glycoxidation, acetylation and methylation (Manzi et al., 2000, Zasloff, 2002). Over half of all proteins are glycosylated (Van den Steen et al., 1998). No modification is exclusive, so multiple isoforms of the "same" protein, distinguished by different combinations of modifications and groups of modifications, can co-exist (Lane and Beese, 2006, Norregaard Jensen, 2004).

Glycoforms of a protein are sugar-modified variants of the same primary amino acid polymer. The three main post-translational protein modifications that use sugars are N- and O-linked glycosylation and glycosyl phosphatidyl inositol (GPI) anchors (Van den Steen et al., 1998). Linkage to the polypeptide is made at serine, threonine and hydroxylysine amino acids (O-linked) or via the amide nitrogen of asparagine (N-linked) (Bardor et al., 1999, Mitra et al., 2006).

3.2.2. Contamination of the food supply

One of the main risks of animal biopharming involving cows is the possibility of biopharm milk entering the food supply. This could have effects on human health, the dairy industry's ability to export milk, and the ability of consumers and producers to decide what to purchase or sell.   The U.S. National Research Council (2002:54) recommended excluding animals from biopharm operations from the food chain.

There has already been at least one case of possible inadvertent contamination of the food supply by animal biopharming. In 2001 to 2003, the University of Illinois released 356 pigs, which were part of their transgenic biopharming experiments to produce certain proteins in the milk of sows, to livestock dealers. The university argued that the pigs did not contain the genes of their parent stock nor were they old enough to be lactating; however, investigations by the FDA found that records were inadequately kept and they were unable to verify this (*FDA investigates improper disposal of bioengineered pigs,* 2003).

Producing biopharmaceutical milk raises further issues. As the valuable protein is produced in the animals' milk, and animals lactate in order to feed offspring, it is not possible to produce the milk without the birth of new offspring. Transgenic animals will essentially be worthless if not needed for the herd and not welcome in the food chain. It is not unlikely, therefore, that biopharm operators will seek approval for excess animals to be permitted in human food or animal feed (U.S National Research Council, 2002: 54). There may be similar attempts to derive value from the milk from biopharm animals that is not required or suitable for pharmaceutical production.

The following examples may shed some light on the potential costs of contamination of the food supply with biopharm products. Although they involve plants rather than animals, they are indicative of the types of costs resulting from contamination and shed some light on this risk in relation to animal biopharming. In 2000, GM Starlink corn, which was not approved for human consumption, was detected in human foods in the United States.[12]   It cost approximately US$1,000,000,000 to recall the contaminated food, clean the processing and storage facilities, and settle lawsuits (Smyth, Khachatourians & Phillips, 2002). Japan temporarily ceased importing U.S corn from October 27, 2000, until they were confident that testing mechanisms for Starlink were adequate. It has been estimated that the Starlink episode resulted in losses of between $26 and $288 million dollars for producers in the U.S. (Schmitz, Schmitz & Moss, 2005). [13]

In 2002, ProdiGene was fined US$250,000 for contamination of other crops with a biopharm corn.

---

[12] The Starlink gene Cry9C was found in a sample of Taco Bell shells on September 18, 2000 (Schmitz, Schmitz & Moss, 2005). The gene was detected later in other foods.

[13] Mullholland et al. v. Aventis Crop Science USA Holding, Inc. was a case filed by non-Starlink corn growers who claimed damages from contamination. This involved loss of market value as well as storage and transportation costs resulting from contamination (Schmitz, Schmitz & Moss, 2005: 392). The case was settled for $110 million in 2003.

> [T]est plots of [biopharm] corn [were] being raised under contract by local growers, one farm in Nebraska and another in Iowa. In the Nebraska case, officials realized that some 500,000 bushels of harvested soybeans were contaminated with small amounts of GM corn, which had been grown during 2001 on the same plot, because the farmer did not weed "volunteer" plants from the field in which the soy was grown. In Iowa, federal officials required a local producer to destroy some 155 acres of corn because it could have been cross-pollinated by ProdiGene's engineered corn being raised in a nearby field. (Fox, 2003:3)

The settlement reached with the USDA also required ProdiGene to reimburse the USDA for the costs of cleaning up the contamination and to post a US$1 million bond (Fox, 2003).

In August 2006, as harvesting began, many American rice growers discovered through an announcement from USDA, that they had inadvertently planted rice contaminated by Bayer's GM rice resistant to its herbicide Liberty. This rice had never proceeded beyond testing between 1998 and 2001 and had never been approved. The company selling the seed rice, Riceland Foods, had first heard of the problem in January and tested seed and found it positive. They had tested again in May and again received positive results which were confirmed by Bayer, but had not notified farmers. Different groups of farmers proceeded to file class actions against Bayer Crop Science and Riceland Foods (Verderosa, 2006; Bennett, 2006; Farm Futures, 2006).

3.2.3. Gene transfer

Large animals are regarded by some as safer to use in biopharming than smaller animals or plants because they are easier to contain (Pollack, 2003: 59). Larger animals are easier to see, and therefore escapes are easier to detect and escapees are easier to catch. Escape poses the risk that the biopharm animal(s) will breed with non-biopharm animals and potentially disseminate the transgenes and their associated epigenetic effects. Some animals (such as cows) have also been argued to be preferable to plants for biopharming in some contexts because of the absence of wild populations of animals with which they could interbreed (Clark & Whitelaw, 2003: 832).

However, the risk of horizontal (or lateral) gene transfer (HGT)[14] is also potentially an issue of concern, as the genetic material that "programmes" the expression of the recombinant protein, may also be contained in blood, secretions, faecal matter and other waste material. This could be ingested or spread by other organisms or animals. For example, blood-sucking insects (Kidwell, 1993; Houck, 1991) or soil bacteria (Heinemann, 2004) could become affected by, or vectors for the spread of, the altered genetic material. This is debated within the risk assessment field. The National Research Council suggests, "Although there is no example yet of acquisition of any gene, including drug resistance markers, by bacterial flora living in a transgenic animal, the

---

[14] The transfer of genetic material other than from parent to offspring.

spread of introduced genes remains a possibility, albeit remote" (U.S National Research Council, 2002: 52).

The fact that horizontal gene transfer has been found to be a substantial contributor to genome evolution may suggest that the possibility is less remote than was once thought. This is unambiguously the case for prokaryotes (i.e., bacteria) (Heinemann, 1999; Heinemann, 2004), and genes in eukaryotic genomes (including multicellular organisms such as humans) owe their origins to HGT or the vectors of HGT (de la Cruz, 2000; Doolittle, 1999; Gogarten, 2005; Syvanen, 2002; Dunning Hotopp et al., 2007). A recent study by Dunning Hotopp et al. (2007) has demonstrated widespread transfer of bacterial genes into the genome of numerous invertebrates. Some believe that it is a serious risk that has not been studied sufficiently or taken seriously enough to date (Heinemann, 2007).

The "generation of potentially pathogenic viruses by recombination between sequences of the vector used to introduce a transgene and related, but non-pathogenic, viruses that might be present in the same animal" (U.S. National Research Council, 2002: 52) is one possible outcome of horizontal gene transfer. It has been demonstrated in principle using tissue culture cells infected by a natural and a genetically modified vaccine virus that gave rise to different recombinant offspring viruses (Hansen, 2004).

Interactions between "natural" viruses and the elements of transgenes are already well documented in plants, and there is no scientific basis for not expecting similar types of genetic interactions to occur in animals. For example, when two genes run by homologous promoters come to be together in the same plant cell, both genes may be silenced. This can result in inadvertent silencing of agronomic traits. Bhullar et al. (2003: 988) note, with reference to the cauliflower mosaic virus [CaMV] 35S promoter, which has been widely used in transgenesis, that "repetitive use of the same promoter is known to induce transgene inactivation due to promoter homology".

Al-Kaff et al. (2000) showed directly that infection of susceptible plants with CaMV can cause silencing of a herbicide tolerance transgene with a 35S promoter. The silencing effect is caused by dsRNA-mediated mechanisms which are conserved throughout the plant and animal kingdoms. Moreover, in non-mammalian animals, the effect has been demonstrated to be heritable (Cogoni, 2000).

Further, as noted above, prion proteins are protein aggregates that transmit a trait as if they were based on DNA. Aggregates of proteins can be extremely stable. Prions are known to persist through conditions that would normally denature the same protein that was not in aggregate form, including autoclaving. In the case of chronic wasting disease (CWD) in cervids (deer family), prions persist in infectious form for at least two years in the soil on land previously inhabited by infected deer (Johnson, 2006).

This raises an important point in relation to HGT: prions and other types of molecules that form epigenes must be considered along with the better known agents composed of DNA. However, research of this kind lags far behind work on DNA and RNA viruses.

Nevertheless, epigenetic engineering is rapidly becoming a reality. Recently researchers from both China and the US seed company Monsanto demonstrated that dsRNA can be infectiously transferred through food to gut cells in insects, and subsequently spread within the animals (Baum et al., 2007; Gordon and Waterhouse, 2007; Mao et al., 2007). Regardless of whether the dsRNA is created by design or by accident, it is now clear that it can have significant biological impact. This issue is of particular relevance to biopharming, because dsRNA is also a potential therapeutic (e.g. O'Neill, 2007, Osborne, 2007, Zhou et al., 2004).

The possibility of HGT may limit the kinds of pharmaceutical substances that can, or should, be produced through biopharming. According to MoRST (2005: 70), animals could also be a source of new classes of antibiotics that could overcome the growing problem of bacteria resistant to conventional antibiotics. However, through horizontal gene transfer, the farming of animals modified to contain antibiotic substances in their blood, flesh or secretions could in fact aggravate the problem of antibiotic-resistant bacteria by encouraging resistance in populations of soil bacteria or bacteria that are the animal's natural commensals (which may often contaminate food produced from the animals). The degree to which this may be a problem will depend on the scale of the biopharming operations and the longevity of the animals. Other constructs with antimicrobial properties, such as recombinant human lactoferrin, may pose similar risks. (Many therapeutic compounds have antimicrobial properties in addition to their intended action [Heinemann et al., 2000].)

The implications of HGT for the feasibility of biopharming may be significant, impacting on all movement off the property, including stock, waste and carcasses, equipment, baleage, vehicles, etc. Other issues involve the flow of ground and surface water (including the impacts of irrigation and flooding) and blood-sucking insects (Nature Biotechnology, 2002).

3.2.4. Animal welfare

It is acknowledged that there are significant animal-welfare problems associated with the methods used to generate biopharm animals (Keefer et al., 2007; Laible & Wells, 2007; PEW, 2004; Dove, 2000; Fiester, 2005). Studies in a range of species have shown that "many clones display various abnormalities" (Laible and Wells, 2007: 105). These abnormalities result in the high mortality rates mentioned earlier, but can also result in health problems for surviving animals: "[a]berrations that occur early in embryonic, placental or foetal development may not necessarily prove lethal but may impair health in adulthood" (Ogura et al. 2002; Loi et al. 2006, both cited in Laible and Wells, 2007). They can also generate health problems for the cloned animals' offspring (Wilmut et al., 2002, cited in Laible and Wells), that is, the unintended pathological changes can be transgenerational. These aberrant patterns of gene expression in clones, say Laible and Wells (2007:103) raise "animal welfare concerns that currently limit the acceptability and the applicability of the technology."

Many cloned and transgenic embryos suffer from "large calf syndrome", a developmental phenomenon that was first noted in nuclear transfer methods used in cattle (Dove, 2000:

1047; Laible & Wells, 2007: 106; Fiester, 2005: 332).   This syndrome causes dystocia, or difficult birth, for the incubating animal. If the calf is not delivered through caesarean section it can cause suffering and death for the cow and/or the calf. Cows giving birth to cloned calves also demonstrate both prolonged gestation and less preparation for parturition (Laible & Wells, 2007: 105-107).

Also of concern is the much-increased tendency for cows to develop hydroallantois, or hydrops. This develops in the second half of gestation; it usually renders the calf non-viable and requires induced abortion to protect the cow. While hydrops occurs naturally in around 0.02% of bovine pregnancies and in about 0.07% of artifical insemination and 5% of IVF cases, with clones the rate is typically 25%. In response to this, efforts are underway to develop techniques for identifying non-viable pregnancies at an earlier stage (Laible and Wells 2007: 106).

Cloned animals are more prone to musculoskeletal abnormalities and, perhaps particularly significant for biopharming, compromised immune systems. As noted above, abnormalities may not reveal themselves before the animal enters a production system, while some epigenetic aberrations may not show themselves in any obvious "external" or phenotypical way (Laible and Wells 2007: 105-6). (On these and other animal welfare issues see also MoRST, 2005; Fiester, 2005: 332; and Dyck et al., 2003; and FDA, 2007.)

Other animal-welfare problems can arise when animals are engineered to produce substances that may in themselves affect the animal.

> [C]ertain bioactive proteins produced in milk can have adverse affects on the animal's health. This is particularly true when they are produced at high concentrations and the protein can be reabsorbed. This limits the use of this type of recombinant protein production system [i.e., animal biopharming] to inactive or non-interfering proteins" (Dyck, 2003: 395; see also Echelard et al., 2006: 37).

Laible & Wells (2007: 116) provide the example of an antimicrobial in milk which has "the potential to compromise the biological function of milk as a food to rear young or for other processing applications" and cites the expression of a particular agent in mice which delayed the "mammary development postpartum and [resulted in] lower growth rates in suckling pups". This limitation on the kinds of proteins that can be produced through animal biopharming is said by some (e.g., Toledo, 2006) to be an argument in favour of focusing on other production platforms.

Chapter 4: Scenarios for Biopharming in New Zealand

A robust assessment of potential benefits and harms of biopharming requires knowledge of relevant practices, and practices are in part the product of ownership and operational factors. This chapter presents a discussion of those factors and nominates four representative ownership/operational scenarios for commercial biopharming in New Zealand. Commercial biopharming will have to abide by any conditions imposed by ERMA; we also, therefore, describe what those conditions are likely to be. This is derived from the conditions ERMA has imposed on biopharm field trials.

Many of the people we interviewed from government and some from CRIs were supportive of the idea that if biopharming becomes viable, it will probably occur in New Zealand. As already noted, AgResearch has signed an agreement with Netherlands-based company Pharming (NV) to work toward the commercialisation of recombinant human lactoferrin produced in cows' milk. It is intended that AgResearch will develop the capacity for market-scale production of the protein; the partnership also involves the development of biopharm protein purification capabilities within New Zealand. AgResearch has received approval by ERMA to field-test biopharm cows under a previous decision given in 2002 to allow the development of GM cattle for non-commercial purposes. ERMA, however, has not (yet) given AgResearch approval to develop commercial herds of the transgenic cows, as several sources suggest AgResearch plans to do (Atkinson, 2005; Pharming NV, 2005; Taylor, 2005; Suttie, 2007).[15] It appears that AgResearch plans to seek approval for commercialisation in 2008 (Suttie, 2007).

Before turning to specific ownership and operational factors, we note that any commercial biopharming scenario would presumably depend upon the following requirements being met:

1. There has been a reduction to an acceptable level of the animal-welfare problems associated with the production of transgenic animals.
2. Sufficient funding or venture capital has been attained and/or strategic alliances formed to provide the investment required to see the product through to commercial production.
3. Clinical trials have demonstrated the claimed efficacy or equivalence of the product to the satisfaction of the appropriate regulatory agencies.
4. The processes of production and purification have been approved by the relevant regulatory agencies

---

[15] For example, a press release by Pharming (NV) commenting on its commercial agreement with AgResearch states, "AgResearch shall bear costs associated with the initial production of rhLF [recombinant human lactoferrin] and support the commercialization of rhLF through its extensive network in the South Pacific and Asia. (Pharming Group N.V., 2005)".

5. The production process is capable of producing commercial quantities of the pharmaceutical substance satisfying the required standards for purity.
6. The biopharm animals have been approved for conditional or general release by ERMA.

4.1. The biopharming enterprise

The following discussion presents the major variables relevant to the shape of the commercial biopharming enterprise in New Zealand.

4.1.1. The animals most likely to be used

A number of different animals can potentially be used as "bioreactors" to produce biopharmaceuticals. The type of animal used will naturally have an effect on the size and production structure of each operation, as well as the actors and social practices involved.

4.1.1.1. Dairy Cattle

As has already been noted, it is argued that New Zealand has certain attributes which would favour the production of biopharmaceuticals through the milk produced by dairy cows. In summary, the reasons are the freedom from TSE diseases, the biosecurity system that protects this status, the research expertise in cloning and transgenic cattle, and the farming and management experience, as well as existing infrasture, for dairying.

It is likely that considerably fewer cows will be needed to produce pharmaceuticals than are used in traditional dairy operations. The size of the herd will depend on the demand for the drug as well as on the concentration at which the biopharmaceutical substance is produced in the milk. For example, it is estimated that a herd of 25 cows genetically modified to produce human insulin could produce enough to provide for Argentina's 1.5m diabetics (RSNZ News, 2007a). The size of the herd, in turn, will affect what management system is required.

4.1.1.2. Goats

Although our interviews with scientists indicated that there no research was being conducted in New Zealand on biopharming with goats, internationally goats have become the first animal approved for commercial production as bioreactors (see Table 1). As noted earlier, the European Medicines Agency has approved the marketing of recombinant human antithrombin produced by GTC Biotherapeutics from biopharm goats in the US. In a late 2007 communication that explicitly cited this decision, AgResearch announced its intention to expand its biopharming activities to include goats (Suttie 2007).

As goats produce less milk than cows (on average 600 to 800L per natural lactation per doe) (Echelard et al., 2006: 40), it is likely that more goats will be needed for production than cows. According to Echelard et al. (2006: 40):

> [A] few hundred transgenic does can … easily yield several hundred kilograms of purified product per year. This level of production can meet the manufacturing needs of several factors traditionally derived from plasma fractionation and for a large number of recombinant antibodies currently in development.

If this is the case, production methods and ownership structures could differ from those for cows. The number of goats needed for the operation could be similar to the size of the typical New Zealand goat farm. As of 2002, there were roughly 150 goats per goat farm in New Zealand(Meat and Wool New Zealand, 2005: 1).

One interview with a member of the Goat Breeders Association indicated a move toward indoor facilities for goat farming. This has become a popular way of farming goats as it controls for infestations of intestinal worms, for which goats do not have a natural immunity. Thus, it may be likely that biopharm goats would be kept indoors.[16] The fact that wild goats are still prevalent in some parts of New Zealand may result in a requirement that biopharm goats be kept indoors in order to reduce the risk of escape and interbreeding.

Whilst interviews indicated that the Dairy Goat Co-operative is not currently interested in this option, there was no indication that it has been completely rejected for the future. However, goat-milk producers currently supply some sensitive, higher-value markets, such as that for infant formula, and our interviewees indicated reluctance to embark on any form of production that might jeopardise their access to those markets. The needs of the Dairy Goat Co-operative will presumably be considered in relation to AgResearch's application to ERMA to biopharm goats.

4.1.1.3. Sheep

Currently there are no transgenic sheep in New Zealand. It is not clear whether field tests will be attempted again using sheep. While AgResearch's recent announcement of its intention to expand its research and development of transgenic animals encompasses sheep, to this point references to biopharm animals have been limited to cows and goats (Suttie, 2007). It is uncertain whether the PPL experience exerts a positive or negative impact on the likely development of the use of sheep for animal biopharming in New Zealand. One interviewee viewed the PPL experience as having demonstrated "proof of concept", providing a basis for future developments. Although New Zealand does not have a strong sheep-milk sector, it does hold expertise in the farming of sheep.

---

[16] The GTC Bioteherapeutics' goats are housed indoors but are able to spend time outside in pens (Redherring, 2006).

4.1.1.4. Chickens

Currently there are no commercial biopharm operations using chickens; however, scientists at the University of Georgia in Athens have worked with chickens in order to express new enzymes in eggs, albeit in small quantities (Pickrell, 2002). There are several advantages to using chickens for transgenic operations. Firstly, there are well-established methods for extracting the protein from eggs, and some scientists predict the process will be much the same for transgenic eggs (Pickrell, 2002). Half of the protein in egg white, ovalbumin, can be used to produce therapeutic recombinant proteins (Lillico et al., 2007). Secondly, reproduction times are shorter and reproduction rates are higher than those of the mammals discussed above (Pickrell, 2002; Harvey et al., 2002). Lastly, it is suggested that "glycosylation patterns of IgGs [immunoglobulin G] in chickens in some aspects resemble those in humans more than do those of goats, cows and sheep" (Harvey et al., 2002: 397).

Poultry have not been easy subjects for transgenesis (Dyck et al., 2003: 395), though more recently Ivarie (2006) contended that this is changing. Researchers have successfully produced a humanised antibody for the treatment of advanced melanoma and interferon beta-1a from eggs (Lillico et al., 2007).

Our interviews suggested that the lack of poultry research in New Zealand makes it unlikely that poultry will be developed for biopharming here. This may not, however, preclude a New Zealand operation carrying out contracted production with chickens supplied by the overseas contracting company.

*

During the course of this research, many factors pointed to dairy cows as the most likely animal to be used in any biopharming operation in New Zealand. Our scenarios are built upon this assumption. However, in light of the recent AgResearch announcement and the Atryn decision, the use of goats has also become a strong prospect. Key factors additional to those considered in our scenarios that should be taken into account in relation to biopharming goats include: the size of the biopharm herd in relation to conventional farm operations and the implications of this for ownership/management structures; the implications of goat biopharming for access to existing markets for high-value conventional goat-milk products; the presence of feral goats in New Zealand and its implications for containability; and the possibility of keeping biopharm goats in indoor facilities and the implications of this for the relative risks associated with horizontal gene transfer. Finally, given New Zealand's capacity and expertise in sheep farming and its freedom from scrapie and TSEs, the possibility that sheep will be used for biopharming in New Zealand also cannot be excluded.

4.1.2. Production and maintenance of a biopharm herd

Every ownership and operational scenario requires the production and maintenance of a biopharm herd. As discussed in Chapter 3, the technology necessary for this is still under

development. It appears that in its biopharming research, AgResearch has been experimenting with various combinations: transgenic semen x conventional cows, transgenic semen x transgenic cows, and conventional semen x transgenic cow.[17] More recently (see section 2.3), their work has included the implantation of imported transgenic embryos into conventional cows.

Biopharm founder animals are produced through the creation of transgenic embryos that have been transfected with the human genetic construct for the production of the required protein. These embryos are implanted into conventional recipient cows. Successful offspring animals can then be cloned, or, presumably, be allowed to reproduce naturally or through artificial insemination. The semen from transgenic bulls can be used for artifical insemination with conventional cows (*in vivo* fertilisation) or for *in vitro* fertilisation to produce transgenic embryos. Conversely, transgenic cows, similarly produced, can be used with conventional or transgenic semen. As noted, transgenic embryos could also be imported, then implanted into conventional cows in New Zealand.

If pregnancy is intended only for the purpose of inducing lactation in the transgenic cow, it may be irrelevant whether the semen is conventional or transgenic. It is not clear at this stage whether techniques for artificially inducing lactation are feasible or likely to be used. If pregnancy is used to induce lactation, most of the resulting calves would likely be aborted or destroyed after birth, particularly if they are male; female calves not needed for replacement purposes may also be destroyed once the desired herd size has been reached. Thus, disposal of unwanted offspring would remain a significant part of ongoing biopharm operations.

4.1.3. Type of farming operation: separate or combined?

A biopharming operation could be included within a larger conventional operation, with biopharmed cows being kept separate for milking purposes in the same way that cows receiving antibiotics or cows producing colostrum are kept separate now. Biopharm cows could be tagged in such a way that they are recognisable, or they could be run as a separate herd brought in for milking before or after the conventional herd, or milked in a separate facility altogether.

The alternative scenario is that of a completely self-contained farm with only biopharm animals for milk production. However, if it produced its own replacement animals, such a farm may have a mix of conventional and transgenic stock, because conventional recipient cows are often used as surrogate mothers for cloned transgenic embryos.

4.1.4. Nutriceutical or pharmaceutical?

As noted in Chapter 3, biopharming may be used to produce compounds marketed as nutriceuticals (food or food extracts claimed to have added health benefits) rather than pharmaceuticals. Interviews with key actors indicated that the decision to produce

---

[17] See the documents associated with ERMA applications GMF98009 and GMD2028, available through the ERMA website (www.ermanz.govt.nz).

nutriceuticals may come down to economic considerations: e.g., relative costs of development, size of the market and premium obtainable.

It is thus relevant to note that in early 2006 Pharming NV, with whom AgResearch has contracted with the aim of producing recombinant human lactoferrin (rhLF) in cows, filed a Generally Regarded as Safe, or GRAS, notice with the USFDA. [18] The notice is for the use of rhLF in functional foods. The FDA has not yet responded to the notice. [19]

Pharming's chief business officer said in 2006:

> We're talking to some manufacturers and nutritional companies in the US about the possibilities of using it as a standalone product or an ingredient in foods. A lot will depend on the partner, and relate to the end product. It may require additional end studies, for example if it is used in infant foods. (Quoted in Patton, 2006)

The majority of existing sales of bovine lactoferrin are in Asia,

> where lactoferrin supplements are common and dairy companies fortify yoghurts with the protein. This market is also likely to be more accepting of Pharming's technology….The company may need to reassure future partners in Europe and the US about the safety of this technology although Singh is confident that attitudes are changing. (Patton, 2006)

AgResearch's agreement with Pharming includes "support[ing] the commercialisation of the ingredient in the South Pacific and Asia" (Taylor, 2005). Thus there appears to be good reason to anticipate nutriceutical-oriented commercial biopharming initiatives in New Zealand. (See also the promotion of nutriceutical/functional food production in the report of the Food and Beverage Task Force [2006] and recent FRST funding.)

---

[18] The GRAS notification program is a voluntary procedure that "is intended to replace the GRAS affirmation process by providing a mechanism whereby a person may inform FDA of a determination that the use of a substance is GRAS, rather than petition FDA to affirm that the use of a substance is GRAS" (FDA, n.d.,b). Freese (2007: 15-16) describes the ensuing process as follows:

> If FDA has no questions, it issues a letter of no objection, which explicitly notes that the manufacturer bears responsibility for the safety of the new ingredient. If FDA has concerns regarding the safety of the ingredient, it informs the manufacturer of the outstanding issues, which must be addressed to FDA's satisfaction…. The major weakness of the GRAS process is the reliance on company-prepared "summaries" of studies they have conducted, which often present only results and lack crucial methodological details needed for a critical evaluation.

According to FDA, its acceptance of a GRAS notification "is not an approval" (FDA, n.d., b.). Why make a GRAS notification? "You may market a substance that you determine to be GRAS for a particular use without informing FDA ... We recognize, however, that some firms prefer to know that FDA has reviewed its notice of a GRAS determination, without raising safety or legal issues, before marketing." (*ibid.)*

[19] In December 2004, Ventria Bioscience filed a GRAS notification with FDA for rhLF for use in foods, beverages and medical foods. Two years later it withdrew the notice. In its letter announcing the withdrawal, FDA notes: "Although you have withdrawn your notice and FDA has ceased to evaluate the notice, FDA, nevertheless, plans to engage the wider scientific community for further consideration of the complex scientific issues in your notice." (Accessed at www.cfsan.fda.gov/%7Erdb/opa-g162.html)

It is not yet clear what this will mean for biopharm farming operations. On the one hand, GRAS status may lead to the conclusion that health hazards from contamination of the food chain are minimal and thus to the downgrading of containment requirements. (However, as GM food is required to be labelled as such in New Zealand and in many export markets, segregation would still be required.) On the other hand, as already noted, many such substances (including rhLF) have antimicrobial properties, suggesting that risks associated with HGT may remain.

4.1.5. Ownership

The operation of animal biopharming will be dependent on the management and ownership structures in place. There are three basic stages in the production of a biopharmed pharmaceutical, which present different ownership possibilities. First, the transgenic animals have to be produced. Second, these animals are farmed to produce the raw unprocessed form of the product. If this is milk, then the process of farming involves not only the feeding and care of the animals, but also milking them and keeping them lactating. Third, the raw product is taken somewhere to be purified and processed or formulated into a marketable product. Each of these stages could be carried out by the same or different owners or organisations, and each could be carried out in different places from the rest or at the same place.

In summary, there could be different permutations and combinations around the ownership and operations of:
1. production of animals and replacement stock
2. farming of animals and production of raw product
3. processing from raw to saleable product.

4.1.5.1. Who owns the animals?

Our interviews indicated that it is most likely that animals will be owned by the developer (a biotech or pharmaceutical company) that produces them, while managed by farmers under contract. However, other options are possible, such as individuals or groups of farmers organising themselves to own the cows, again working with a particular biotech or pharmaceutical company, but on a somewhat different footing, as is done with share milking at present.[20] (Share milking involves a situation in which the herd and the farm have different owners.) One issue that may be important for assessing biopharming in practice, then, is whether the farmer/manager of the herd is also its owner.

The type of owner may also be relevant: e.g., an individual or family, a cooperative, or a large corporation. In terms of assessing benefits to New Zealand, it may also be relevant whether the operation is New Zealand- or overseas-owned.

---

[20] Noelle Muggli-Cockett of Extension and Agriculture at Utah State University suggests that "transgenic animals that produce pharmaceutical proteins can be managed by small producers and provide a new revenue stream" (PEW, 2005: 7).

4.1.5.2. Who owns the land?

A related issue is whether the owner of the herd also owns the land on which it is farmed. Various ownership types and combinations will produce different distributions of profit (relevant to assessing benefits) and of responsibility or accountability for management of the farm and of the herd (relevant to assessing and managing risk). The land on which the animals are farmed could also be owned in different ways – by a corporate, by a group, or by an individual. The owners involved may or may not be farmers, in the sense of being responsible for the day-to-day running of the farm.

4.1.5.3. Summary of ownership/management possibilities

- Farm manager, corporate ownership – farm and animals are owned by a corporate entity which employs a manager to manage the everyday running of the farm.
- Farmer owns and manages the farm and the animals, producing on contract to a biotechnology or pharmaceutical company.
- Farmer owns the operation but is subsidised for containment and safety costs - to be accessible to farmers, containment and management costs could be subsidised by a larger company.[21]
- A coalition of farmers within a geographical area owns and manages the operation, producing on contract to biotechnology or pharmaceutical corporation.
- A self-contained commercial research enterprise produces the transgenic animals, farms them, and produces the product (the GTC Biotherapeutics model).

With the exception of the last option, the assumption here is that purification would be carried out off-farm, by a separate enterprise. The possibility that purification may be carried out on-farm introduces yet another variable.

4.1.6. Four scenarios

The following four combinations of ownership and operational variables appear to be the most likely scenarios under which commercial biopharming would be carried out in New Zealand. All farms would have to meet requirements for containment and audit (discussed below). These scenarios will be examined in the next chapter for their practicability in the light of our interviews with farmers.

Scenario 1: Farmer-owned and –operated mixed farm

This scenario would follow the more traditional New Zealand model in which the farmer owns both the animals and the land and is also the primary farm operator, perhaps with the help of the farmer's family and/or one or more farm labourers. The farm would include both a small transgenic biopharm herd and a conventional dairy herd. The transgenic animals would be sourced from a specialised transgenic animal production operation with a licence to produce certain transgenic animals. The conventional animals

---

[21] One of the dairy companies whose personnel we interviewed indemnifies their farmers for taking on the risk of a new product, so that they are not disadvantaged in relation to other farmers.

would be sourced in the usual way, through the farmer's own breeding of replacements or from sales. The conventional milk would go to the local cooperative dairy factory and the pharmaceutical milk to the processing facilities of a private pharmaceutical company.

Scenario 2: Farmer-owned and -operated specialist biopharm

In this scenario a farmer would own the land and the animals and would be responsible for the whole farming operation. The farm would have only biopharm animals and would buy its replacement animals from a specialised transgenic animal production operation. The milk would be sold to a private pharmaceutical company for processing.

Scenario 3: Corporate-owned, employee-managed biopharm

In this scenario a corporate would own the land and the animals and would employ a manager responsible for the whole farming operation. The farm would have only biopharm animals and would buy its replacement animals from a specialised biopharm animal production operation. The transgenic milk would be sold to a private pharmaceutical company.

Scenario 4: Self-contained integrated biopharm

This scenario reflects the organisation of GTC Biotherapeutics. This farm would produce its own animals in its research facility, farm them to produce transgenic milk, and process the milk to extract the compound. The compound could then be sold to a pharmaceutical company or, if the biopharm owner is a pharmaceutical company, be developed and marketed by the same company.

4.2. Controls

A commercial biopharming operation in New Zealand would require ERMA approval. "Conditional release" was added to the categories of possible ERMA approvals in 2003 (New Zealand. Environmental Risk Management Authority, November 2003). Previously applicants could apply only for containment, field test or full commercial release. Full commercial release means that the product requires no controlling or monitoring. Conditional release allows a new organism to enter the environment under certain specified management and/or monitoring conditions. We assume here that any application to ERMA for a commercial biopharming operation would be made under the conditional release category.

It is useful to postulate what the ERMA conditions (controls) are likely to be when developing biopharming scenarios. The controls may affect who can own a biopharm operation, for example, as compliance with controls may be impractical in some circumstances or may raise establishment and running costs significantly. Controls may also have an impact on the type of farming operation that can be implemented—for example, whether biopharming can be combined with conventional farming. Finally,

postulating the ERMA conditions makes it possible to identify holders of knowledge that may be relevant to assessing the practicality, risks and likely effects of the conditions.

ERMA has not yet approved any applications for commercial biopharming; however, they have approved several field tests. These approvals have come with conditions placed on the operations. The primary purpose of these conditions is to ensure containment of the animals and their products. We draw on the documentation of conditions imposed on field tests to outline the containment requirements that are likely to be imposed on any biopharm operation in New Zealand. In particular, we assume that ERMA would impose conditions similar to those required by its approvals of AgResearch's applications GMF98009 and GMD02028. (The latter is technically a "development" rather than a "field test" application; however, in terms of its proposed outdoor activity it appears to differ little from the field test application GMF98009. [22])

4.2.1. Physical containment of biopharm animals and their products

4.2.1.1. Containment of animals

The most obvious form of containment is the physical containment of the biopharm animals themselves. ERMA has required with regard to existing biopharm research facilities that the outdoor containment facility be enclosed by a two-metre-high double perimeter fence with an inner fence electronically monitored and alarmed to enable location of any breach of containment. The fence should be constructed in accordance with MAF's *Containment Standard for Field Testing of Farm Animals,* which prescribes the materials to be used and the method of construction. It also mandates that the area between the two fences shall be clear, "so that if animals gain access they can be easily seen".

In the event containment is breached, ERMA has required that the operator recover the escaped cattle. If there has been any possibility of mating during the escape, affected cows must be destroyed or any pregnancies that may have resulted from the escape aborted. Presumably this applies to neighbouring conventional cows (in case of an escaping bull) as well as to any escaping biopharm cows. The MAF inspector responsible for the facility must be notified within 24 hours.

The ERMA approvals require that no genetically modified cattle, surrogate mothers (cows carrying GM foetuses to full term or near to full term), or recipient cows (cows that receive a GM embryo but subsequently lose the foetus) be permitted to leave the outdoor containment facility except in accordance with the *Containment Standard for Field Testing of Farm Animals.* Permission for this must be sought from the facility's MAF inspector, and any transport of animals must be in a sealable, towable conveyance, which

---

[22] Some of the controls imposed by ERMA on GMD02028 were intended to ensure that the distinction between "development" and "field trial" was maintained. For example: "Breeding shall be limited to the minimum necessary to complete development. No breeding of animals is allowed, except where necessary to ensure that 'true to type' animals have been produced and to investigate stability of inheritance."

must be sealed by the inspector before transfer. The conveyance, including effluent tanks, must be cleaned after unloading. Further, the animals are to be transported directly to the receiving facility and:

> [t]he driver shall be given contact phone numbers in the case of an emergency. A sign shall be displayed in the cab which states: "In the event of an accident or emergency phone these contact phone numbers as soon as possible." These numbers shall be readily available in the cab.

It seems likely that, in order to facilitate containment, limitations would be imposed on the number of animals allowed on any particular farm. It is unclear whether transgenic bulls would be needed or permitted on the farm. It is quite possible that the commercial biopharm operation would not produce its own replacement animals (see Scenarios 1-3 above); if it did, presumably frozen semen from founder bulls could be used through artificial insemination. It may be considered that transgenic bulls would pose the greatest escape risks; given that other less risky methods of replacement are available, controls may involve the exclusion of transgenic bulls.

4.2.1.2. *Identification of animals and facility*

In order to facilitate recapture of escaped animals and to prevent inadvertent contamination of the conventional milk supply through mishandling, there must be robust identification methods for biopharm animals. ERMA currently requires that: all conventional cattle within the facility be double tagged; all genetically modified cattle be individually identified by an ear tag and also implanted with a subcutaneous electronic microchip for individual electronic identification; and in the event that subcutaneous microchips cannot be implanted until cattle reach a certain age, cattle without microchips shall have two different types of ear tags in place at all times to allow for immediate identification. The GMF98009 approval requires that the identification system include a database from which information on individual genotype and generation can be derived, and both approvals require that a register be maintained with records of identity and fate of all cattle in the operation.

The *Containment Standard* also requires that the facility itself be clearly identified: "A prominent sign shall be displayed at the entrance(s) to indicate that the premises is [*sic*] a containment facility and that unauthorized entry is prohibited."

4.2.1.3. *Disposal of carcasses*

ERMA has mandated the method of carcass disposal in all biopharm approvals. In the case of the PPL sheep, this was to be through on-site or off-site incineration. In the case of the cattle research in GMF98009 and GMD02028, it has mandated burial:

> Disposal shall be by burial in unlined offal pits. Offal pits are to be located within the outdoor containment facility and shall be positioned to minimise leaching to groundwater. The applicant shall consult with Ngāti Wairere with respect to

developing culturally appropriate mechanisms and protocols for disposal, which add to and are consistent with the rest of this control. (ERMA 2002)

It has also mandated that "in the event of mortality in genetically modified cattle in the containment facility, carcasses shall be immediately removed to prevent access by scavengers."

In the relevant GMF98009 decision, conventional cows that failed to become pregnant after embryo implantation were permitted to be sold or disposed of off-site 50 days after three negative pregnancy tests administered 28, 35 and 50 days after embryo transfer. Conventional surrogate cows that have given birth to a transgenic calf were also allowed to be disposed of off-site after a withholding period of at least 100 days to ensure that no foetal blood cells remained (ERMA, 2001: 13, 42). In decision GMD02028, however, it was decided that it was not appropriate to distinguish between recipient cows (conventional cattle that have failed to carry a transgenic embryo to term) and surrogate mothers (conventional cattle that have given birth to transgenic calves) for the purposes of disposal – both of these, as well as offspring that are non-transgenic, should be disposed of on-site, through burial in the manner described above (ERMA, 2002: 18-19).

4.2.1.4. Containment of milk

ERMA currently requires that milking take place within the containment facility and that milk be transported in secure containers to a processing facility registered as meeting the requirements of the MAF Biosecurity Authority/ERMA New Zealand Standard *Containment Facilities for Microorganisms.* In addition to containment requirements, a facility for extraction of pharmaceutical substances would be likely to operate under additional requirements for assuring the safety of the product.

ERMA also currently requires that the quantity of milk produced and its fate be logged in a register. Any surplus milk and milk components would presumably be subject to the same prescriptions for disposal that currently apply to all of the milk produced in the approved research, namely: destroyed on site, by an effluent treatment digester, incineration, or spraying onto pasture following treatment to destroy any cells present.

It may also happen that different proteins are produced on the same farm. In this situation cows would need to be managed as separate herds and their milk segregated. This would add on-farm segregation and containment issues even for an exclusively biopharm operation, in the interests of protecting the integrity of the product.

4.2.1.5. Protection of the food chain

ERMA currently requires of approved biopharm research operations that they ensure that no part or product of any animal involved in the operation—including *inter alia* surrogate mothers, recipient cows and non-transgenic calves—enter the food chain or "be ingested by any person at any time".

4.2.2. Containment of genetic material

In its most recent decision, ERMA required monitoring of soil organisms for horizontal gene transfer (HGT; see above, section 3.2.3):

> Micro-organisms shall be tested for the presence of the introduced genetic modifications at the disposal sites. If HGT is detected, genetic modification and disposal of cattle shall be immediately halted and the Chief Executive of ERMA New Zealand informed. A remediation plan to manage the impact of the HGT event shall be developed in consultation with the Chief Executive of ERMA New Zealand. (ERMA, 2002)

If HGT is recognised as a hazard, it is likely that monitoring of micro-organisms will be required at disposal sites, but also potentially farm-wide in consideration of HGT occurring through animal waste. More extensive controls may also be put in place to prevent the spread of soil or animal waste off-farm, such as cleaning protocols or restrictions on movement on and off the farm. This may be particularly likely in the case of biopharming for compounds with antimicrobial properties.

Given the vision noted earlier (see section 3.2.3) of biopharming as a method to produce new antibiotics to *overcome* the problem of antibiotic resistance, and given that many therapeutic substances have inadvertent antimicrobial properties, this may become a significant regulatory issue impacting upon a range of biopharm farming practices, particularly with regard to the disposal of waste and carcasses. However, in light of the many opportunities for HGT presented by outdoor grazing (not only contact with soil and water, but also, e.g., blood-sucking insects), management of this hazard may be found to require that animals be kept in indoor facilities.

Chapter 5: Relevant Practices

This chapter considers the potential benefits and hazards posed by biopharming in the context of current practices in the dairy-farming sector. It will highlight what has been learned from interviews with farmers about practices in the dairy sector that may have a bearing on the scenarios outlined in the previous chapter and, in particular, on the implementation of protocols developed to manage potential hazards.

Interviews were conducted by phone or in person with dairy farmers from Canterbury, Taranaki and Waikato and with goat farmers supplying to the New Zealand Dairy Goat Co-operative. The farmers were selected through a search of dairying websites such as those of Federated Farmers, Dairy Insight and the New Zealand Dairy Goat Co-operative, which had contact details of some farmers. Personal networks of farmers who could suggest potential interviewees were also used, as were suggestions by the farmers already interviewed. We intentionally included farmers with experiences of farming in different areas in New Zealand and also included an organic practitioner. These interviews focused on current practices on dairy farms and how they might impact upon or be impacted by a conversion to animal biopharming.[23]

Farmers were interviewed about current farm practices as well as the challenges farmers face when trying to meet existing (i.e., non-biopharm) quality controls. These discussions highlighted a number of everyday practices in dairy farming that acquire special significance in relation to biopharming. In this analysis, we group these practices into two categories: social influences on rule-following and practical implications for containment.

We note that at least some of the risks and implications identified in these interviews are avoidable through careful planning and considerable spending. However, if they are to be managed, they first must be identified.

5.1. Biopharming on the dairy farm: social influences on rule-following

The literature on local knowledge and risk assessment is littered with examples of individuals not following rules and behaving in unexpected ways (at least unexpected to those looking from the outside), generally making risk management more complex than it may initially seem. Rules and controls are often demonstrated to be unrealistic, impractical or irrelevant in the contexts of application in practice. The inability of authorities to contain Starlink corn (Marvier & Acker, 2005) or the BSE outbreak in the UK, among others,[24] point to the need to understand rule-following from within the

---

[23] This material is occasionally supplemented with insights from the annual reports made by the operators of the AgResearch Containment farm to ERMA as a part of their audit requirements.

[24] Irwin's (1995) account of the dispute between farm workers and the UK Advisory Committee on Pesticides (ACP) over the use of the herbicide 2,4,5-T is particularly relevant here. The ACP concluded

social dynamics of the rule-following context. Complex contexts may favour adaptable practitioners; an appreciation of adaptability may engender resistance to fixed standards and rules (Wynne, 1988).[25]

In our interviews, farmers noted that relying on the prescription of biopharm farming practices (i.e., controls) to avoid harms may be risky. Many of the farmers interviewed suggested that the effectiveness of controls will depend in part on how farmers interpret them and how they feel about them. Given that animal biopharming is likely to be, at least initially, subject to strong controls,[26] the interviews illustrate the importance of looking at farmers' rule-following practices when seeking to gauge risks.

The following section presents the factors, identified through the interviews, that are likely to influence the degree to which biopharming rules are followed.

5.1.1. Ownership

Most interviewees felt that farmers are likely to be more meticulous with and committed to animals that they own. In their view, ownership of animals was associated with a higher level not only of care for the animal but also of attention to rules around managing the animals. Several interviewees regarded the scenario in which a farm-manager would run the farm (see scenario 3) as potentially risky for this reason. However, whilst the majority of farmers interviewed agreed that ownership will affect attitude and in turn may affect willingness to follow rules, one farmer believed farm managers would be particularly capable of performing the proper procedures, because of the training and experience they must acquire before being employed as managers.

that the pesticide was safe, provided it was used "in the recommended way". Farmworkers, with knowledge of actual farm practices as well as of the social (power) relations involved, argued that it could not be judged safe because the prescribed precautions could not in fact be taken in the actually existing contexts of use: "the conditions envisaged by members of the [ACP] ….are impossible to reproduce in the field" (17-18). In the case of Starlink, faulty assumptions about the planting practices of farmers assumed that the segregation rules for GM corn would be easily followed, which thus provided a false confidence in containability (Taylor & Tick, 2000). The BSE example relates to scientific recommendations made to ensure safety of cows that ignored the social realities of meat-industry practices in Britain.

[25] Rosin et al. (2007a; 2007b) found that, despite the importance of compliance with the EurepGAP programme to the kiwifruit industry's marketing strategy in Europe and the high cost of discovery of non-compliance, many kiwifruit producers strongly resented the volume and detail of the paperwork involved in the EurepGAP audit; they did not view compliance as either integral or appropriate to the broader skills of being a good kiwifruit producer, rejecting paperwork and audit requirements perceived to be either repetitive of existing requirements or excessive in regard to the detail of audited practice. (This was not the case, however, among a minority of younger producers.) In a parallel study of the sheep/beef production sector in New Zealand, Rosin et al (2007c) documented an even greater reluctance among sheep farmers to apply assurance scheme protocols, despite often perceiving the potential value of the audited practices. The farmers resented the office-based requirements (i.e., paperwork) which contributed to a range of 'compliance costs' that they saw as being responsible for poor economic performance by the sector. These findings are consistent with the findings from our interviews with the dairy sector.

[26] As stated earlier, this may depend on the classification of the health product the animal is designed to produce. For example, as Pharma (NV) is seeking to classify human lactoferrin as GRAS (Generally Recognised as Safe) through the FDA (Food and Drug Administration, U.S), this may have implications for the level of controls required for that particular product in New Zealand (*Cow-produced Lactoferrin Completes GRAS notification,* 2006).

5.1.2. Farmers' perception of risk

The farmers' own beliefs regarding the riskiness of an operation may affect the likelihood that they will accurately follow controls. That is, if a control is felt to be arbitrary or out of proportion to the risk as the farmer understands it, it may not be followed. This implies that the effectiveness of controls is to a significant degree reliant on farmer discretion.

One interviewee gave as an illustration the example of effluent disposal:

> They think 'oh, this will do'. You know, 'The rules are that strict, but if we do this and this, it might be all right'.

With reference to biopharming, a farmer indicated that prescribed procedures in relation to escapes of biopharm animals from containment may not be followed. The farmer admitted that he would be unlikely to report any escape of biopharm cows onto his farm because he would not want to deal with red tape and potential monitoring requirements for an eventuality he did not believe was a risk. Thus, in the case of an animal escaping onto his farm, he would be likely to return it (or not) without reporting the case, even if this was required to be done by regulation. The requirement to destroy potentially affected animals or terminate pregnancies may reinforce this tendency.

These comments suggest that the effectiveness of containment protocols may depend not only on the biopharming farmer, but on his/her neighbours as well. In this example, protocols around managing escapes may be undermined by a reluctance of neighbouring farmers to comply.

Similar issues were identified in a farmer's discussion of "slackness" around the management of herds containing tuberculosis-infected cows. There are geographical areas where animal movement is restricted and animals must be traceable, but, it was indicated, farmers may just move them without telling anyone. One farmer said it was only a small proportion of farmers who behave like this, but it does happen. It was also noted that ear tags can and do fall out - and may even be helped to do so. This suggests, among other things, that a more permanent and tamper-proof method of identification of biopharm cows may be necessary to maintain segregation and containment.

A number of farmers were also found to be resistant to the idea of clearly identifying any biopharm operation through prominent signage. This was due partly to a different evaluation of the nature and degree of risk and partly to disagreement regarding the strategy for the management of risk. Some felt that signage may attract protesters or otherwise bring unwanted attention.

5.1.3. Economic incentives to flout rules

One farmer suggested that rules are most often ignored when there is an economic incentive not to follow them. In particular, shortcuts may be taken when income is down. For example, if a farmer owns the operation and is responsible for paying to ensure that all controls are met, compliance with controls may be particularly influenced by

economic factors. As with any product, increased market supply or reduced market demand may erode the profitability of the operation. In the case of biopharming, the existence of potentially competing production platforms could bring about sudden increases in supply (and reductions in price), while the complexities involved in the production of biopharm animals may make it difficult to respond to price changes by changing production to a different biopharmed substance. Such pressures experienced by a farmer directly or through his/her employer could provide an incentive not to follow the rules.

5.1.4. Employment issues and human error

Quality of employees, the number of workers employed and high staff turnover rates were all identified as risk areas for animal biopharming. A 2002 report showed that 76% of employees in the dairy farm industry had worked within the industry for over a year. However, only 28% had been in their present job for more than one season (Shearle, 2002: 17). This indicates a high level of job turnover that will have to be addressed by farmers, or pharmaceutical companies, who hire farm managers and farm workers. Training will be a high priority in order to ensure the safety of animal biopharming, but the high level of turnover may make this more difficult and costly. An implication for farmers is that they may have to commit to longer-term employment under an animal biopharming operation. One interviewee suggested it would be particularly impractical for share milkers to be involved in animal biopharming because they tend to move farms every three or four years.

Most interviewees could relate a litany of human error that occurs in everyday farming practice. With regard to animal biopharming, the issue of human error may become more important in relation both to safety and to the economic impact of current liability laws, which decree that liability falls on those who break rules. Thus, securing quality labour was considered by the farmers we interviewed to be vital to the safety and economic success of animal biopharming.

Interviewees cited the example of cows being milked that were not meant to be, simply through lack of communication or concentration. The milk of cows being treated with antibiotics, for example, is meant to be kept out of the milk sold off the farm, and these cows are marked to indicate this. However, our interviewees cited cases of such markings coming off or just being missed by the person responsible for milking. These errors occur despite the fact that Fonterra and other dairy companies impose heavy financial penalties for farmers whose milk contains antibiotics. In fact, the potential for human error in milking cows was considered important enough for all farmers to suggest that biopharm cows be kept entirely separated from non-biopharm cows, or at the very least in different milking chambers.

One of the farmers we interviewed interview suggested that errors are particularly prone to happen on farms with many employees. Changes in shift times and more people on the farm mean that communication becomes difficult and mistakes are made. Another of our interviewees noted the tendency for employees' drinking on certain nights to affect the next day's attentiveness to the job.

Compliance and auditor reports from the AgResearch containment farm also point to the ubiquity of human error. For example, the auditor's reports show that some milk was sent to a destination that had not requested it, the number of embryos imported and used were not correctly recorded, and semen sent off site for processing into straws was not traced correctly. In addition, the staff training file had not been correctly updated and a new staff member had not been trained correctly about the keeping of lab records (Hale, 2006: 46, 56; Operator, 2005: 33). As these examples and the improper disposal of genetically engineered pigs at the University of Illinois-Urbana/Champaign (FDA, 2003) illustrate, even in a controlled situation such as a contained research unit with qualified staff, mistakes are made. Many more opportunities for human error will be present on a full-scale commercial farm.

5.2. Biopharming on the dairy farm: Practical implications for farming practices

Previous chapters have explained the need to contain bioreactor animals, their products and the transgenes they incorporate. The interviewees identified several areas of practice that may affect the ability to contain animals and soil within an animal biopharming operation. Significant changes to farming practice may have to occur to ensure that safety is maintained on the biopharm.

5.2.1. Size of herd

Typical milking facilities are designed to milk hundreds of cows; they cannot, according to the interviewees, be used on small herds, as the quantity of milk obtained from them would not be enough even to push through the milking machinery. This implies that milking small biopharm herds would require the design and installation of new milking facilities, which also incorporate even stricter cleanliness standards, significantly raising the cost of the operation. The interviewees also suggested that the transportation of significantly smaller amounts of milk will result in additional costs and infrastructure requirements, such as smaller tankers that pick up smaller quantities of milk more frequently.

One interviewee also suggested that new technology may allow some processing to be carried out on-farm. This could reduce the volume of the product leaving the farm. Another possibility is on-farm freezing of the milk or semi-processed product, so that it can be sent for purification in larger batches as required. This processing could take place on or off the farm. On-farm processing may in turn limit the impact of transport issues; however, it would raise other investment, containment and hygiene issues.

5.2.2. Grazing patterns

The common practice of off-farm grazing, particularly prevalent in the winter (in some areas of the country), is used to save pasture on the farm for the spring, which is the period of highest demand. This may have practical implications for the controllability

and containment of animal biopharming operations in the future. Depending on the size of the operation, it may be impractical to keep the cows on the same unit all year round. If the farmers were to graze biopharm animals off the farm in the winter, then additional safeguards may need to be implemented during transport of cows and measures may need to be in place to monitor the spread of heritable material to soil microorganisms and possibly to other animals on those paddocks. At the very least, this illustrates that strictly containing animals to one specific area may be a more complex task than it appears, requiring changes to normal farming practices.

The issue of DDT residues in the soil of some farmland in New Zealand was also raised. DDT is insecticide which was widely used from the 1950s until it was found to accumulate in the environment and in organisms within the food chain. Although the levels of DDE, the DDT residue, found in New Zealand soil are expected to be below the level that would cause health problems, the risk and undesirability of the chemical entering the food chain and further accumulation in New Zealand soils was enough to ban its use in 1970 (Hunt, 2004a; Boul, 1994: 257). Winter feed frequently is in the form of root crops or other forage apart from grass, and cows may ingest a percentage of the dirt containing the DDE, which is retained in the animal's fat. During the spring when the cow comes into milk, the first milkings may contain DDE. From this process it is possible that DDE can enter the milk supply This means that some farmers graze their cows on low DDE properties during the winter.

It will be important for controls to be in place to ensure that farms have low enough levels of DDT to ensure that off-farm grazing is not required. Currently, testing is done on farms before they are converted to dairying; however, the levels may need to be lower in the case of animal biopharming operations. Alternatively, biopharm operations would need a low enough stocking rate to avoid off-farm grazing.

5.2.3. Disposal of animals

As already noted, the number of animals needed by an animal biopharming operation will vary according to which pharmaceutical substance is produced and its concentration in the milk. It is consistently predicted, however, that relatively small herds will produce enough to satisfy many biopharmaceutical markets. As pregnancy is necessary to induce lactation, culling will be a significant part of herd management.

Animals regularly destroyed in AgResearch's biopharm field test include transgenic bulls (once adequate stores of semen have been collected; this is required by ERMA), cows that do not express sufficient concentrations of the desired protein, and non-transgenic calves produced in order to initiate lactation. The last category may be particularly relevant to commercial biopharm operations. ERMA requires that these animals be buried on-site and prohibits their sale into the human food or pet food supply (ERMA, 2002).

If these rules apply to commercial biopharm operations, they could, according to our interviewees, pose economic and environmental problems. Some farmers and share milkers derive a significant amount of their income from the sale of bobby calves and the

culling of animals. This would not be permitted under the rules noted above. Our interviewees also highlighted potential impacts on groundwater of on-farm burial of large numbers of carcasses; such impacts would others beyond the biopharm.

5.2.4. Health of animals/excess milk

Because it is likely that biopharm milk will need to be kept at a higher standard of cleanliness, farmers may need to be more than usually protective of the animals' health. Thus the cost of veterinary care can be expected to be considerably higher. It may also be necessary to hold extra animals in case an animal does get sick, in order to ensure continuity of supply. If this is the case, the disposal of excess milk may become a factor. Several interviewees suggested that the practice of spraying unused milk onto the paddock may have to be changed, particularly if this land is being grazed by non-transgenic animals as well. The chance of this milk affecting the soil composition may also be an issue.

5.2.5. Location of the farm

Our interviews with farmers highlighted several factors to do with the location of the biopharm. Interviewees emphasised the importance of soil characteristics. In order to minimise impact on groundwater systems, soils should be deep and free-draining; in order to minimise impact on streams, clay soils, which result in greater run-off, should be avoided.

An aspect of location identified by farmers that may affect the containment of animals is vulnerability to flooding. An interviewee described the level of disorganisation that occurs during a flood, in which normally controlled environments are disrupted, and animals from different farms may become mixed together. The ramifications for containment are obvious. For these reasons, the farmers suggested that animal biopharming should not be permitted in areas that might flood.

5.2.6. Traffic on and off the farm

As noted in Chapter 4, there has been significant debate about the effect animal biopharming may have on soil and its micro-organisms. Many farmers suggested that any need to contain soil would be complicated by various farming processes that effectively require traffic through the farms. The potential for hay bailers and fertilizers to spread soil from one farm to another was identified by the interviewees. It is questionable whether workers applying fertilizer or hay-bailer operators could be expected to clean their equipment thoroughly each time they exit the farm. An editorial in *Nature Biotechnology* questions the wisdom of presuming farmers will follow such meticulous cleaning standards in relation to GM plants; the point may also be applicable here (Nature Biotechnology, 2002: 527).

5.2.7. Fate of biopharm properties

As stated previously, the PPL therapeutics field tests ended with controversy centring on monitoring and future use of the property. Farmers could envision similar problems occurring as a result of current patterns of farm-property ownership in New Zealand. The

high turnover rate of farms, with farms changing hands relatively rapidly, raises issues around post-biopharming use of the land. The interviews suggest that the same issues that arose after the closure of PPL operation, such as the appropriate fate of the biopharm animals and the use of the land for grazing conventional animals, will inevitably arise in this situation. The question of the limitations on post-biopharm uses of the land may be important from a safety perspective and was noted as being important from an economic perspective. The ability to revert to normal dairying was questioned by several farmers. Not only may land that has once been used for biopharming not be suitable for conventional farming again, it may also be difficult for a farmer to get back into a co-operative such as Fonterra. The interviews suggested that such obstacles in the way of returning to conventional farming would make many farmers reluctant to become involved in biopharming.

Chapter 6: Conclusions

This chapter summarises the substantive findings of the research on the types of animal biopharming most likely to be pursued in New Zealand over the next 10-15 years and the practical issues relevant to assessing potential scenarios for animal biopharming. It also presents some preliminary findings on the substantive and methodological implications for assessing and managing the risks of biopharming. (A full report on regulatory and governance implications will be produced later in the project.)

6.1. Types of animal biopharming

If commercial animal biopharming in New Zealand is to capture the value associated with research and development, it would appear that it would need to use dairy cows to produce biopharmaceutical substances in their milk. We base this conclusion on current research programmes[27] and commercial arrangements, as well as on the advantages of cows in terms of the volume of milk produced and the existence of dairying expertise and infrastructure in New Zealand. However, this conclusion comes with several caveats.

First, precisely because dairying is becoming ubiquitous in New Zealand, it may be difficult to find locations meeting all safety criteria that are also sufficiently distant from other dairy herds to mitigate contamination risks. Second, the size of the dairy industry also means that any negative impacts that bovine biopharming may have on the market for non-biopharm milk from New Zealand would have a significant negative impact on New Zealand's economy. Third, should HGT be recognised as a significant risk, either in general or in relation to specific compounds, regulations may require animal biopharming to be carried out in indoor facilities. This would negate some of the advantages noted above (e.g., existing dairying infrastructure and dairy-farm management expertise), and the relatively large size of cows would perhaps become a disadvantage. In this case, attention may turn to goats.

A goat-milk industry exists in New Zealand, and our interviews indicated that biopharming has not been absolutely ruled out. They also pointed to a move toward the use of indoor facilities in the industry. However, interviewees also indicated they would be very reluctant to embark on anything that could jeopardise their success in the sensitive, higher-value markets they currently supply.

There is little evidence of New Zealand-based interest in using sheep for biopharming at this stage, though that does not preclude another PPL-like operation in which an overseas company uses a New Zealand farming operation to produce the compounds they market.

---

[27] As noted earlier, however, AgResearch has announced its intention to expand its biopharm research to include goats and sheep.

Biopharming using other animals—such as chickens, pigs, or even rabbits—if proposed for New Zealand, would most likely take the form of a contract operation for an overseas company. Given the lack of New Zealand-based research on these animals, research, development and (perhaps) purification activities would be likely to be carried out outside New Zealand.

6.2. Feasibility of the scenarios

6.2.1. New Zealand farmers as biopharmers (Scenarios 1 and 2)

Scenarios 1 and 2 envisioned that some New Zealand dairy farmers would become biopharmers. As one of our key actor interviewees argued, existing farming expertise is one of New Zealand's advantages in the animal biopharming arena:

> You would be looking to utilise the knowledge that we have in handling 250 cows with one man and a dog, which we do on our dairy farms….[Y]ou would want to get all the productivity gains that would come from good New Zealand farm practice, but also obviously the significant increase in revenue gains from producing something other than milk.

Our interviews highlighted a number of obstacles to this.

Farmers did not generally think it would be possible to include both biopharm and conventional dairying in the same operation. In their view, it would be necessary for a farm property to be devoted exclusively to biopharming in order to protect the integrity of both biopharm and conventional products. But operating a specialist biopharm would raise further challenges for farmers.

Farmers pointed out that an operation involving a small specialist herd producing a product requiring high levels of segregation and containment would require a dedicated infrastructure: not only dedicated paddocks and special fencing, but also milking and transport infrastructures suitable for relatively small quantities of milk and high levels of containment. Constraints on other practices, such as off-farm wintering, imply being able to afford a higher land-to-stock ratio and buying in winter feed. (This would presumably be affordable if returns to farmers were to increase to the levels predicted by some of our key actors.)

Costs of establishment of a specialist biopharm also include the consequences to the farmer of opting out of their supply relationship with Fonterra, or other cooperative—i.e., it may be difficult or impossible to opt back into that relationship later. This would be a major risk for a farmer to take. Similarly, it is likely that a farmer producing biopharm milk would supply a single company (which is very unlikely to be a farmers' cooperative). This raises risks associated with the considerable power differentials likely to be present in such a relationship and with the fate of the farmer should the company withdraw from the business or go into liquidation.

Finally, farmers also expressed a lack of enthusiasm for the kind of contract operation in which their activities are highly prescribed. They saw this as eroding the autonomy of the farmer to an unacceptable degree.

6.2.2. New Zealand farms as biopharms (Scenarios 1, 2 and 3)

Farmers suggested that there would be fairly extensive topographic and other physical criteria that would need to be met by a biopharm property. In addition to this, there may also be difficulties associated with scaling up biopharm activities from their current research facilities to multiple commercial operations. One of these is disposal of waste. Currently, ERMA controls require that carcasses and surplus milk be disposed of on-site, carcasses through burial and milk through spraying on pasture. Farmers expressed concerns about the impacts of carcass burial on groundwater and thus on neighbouring properties. Such issues related to disposal of carcasses and surplus milk would presumably become more significant in the event that biopharming moves beyond a single research site and into commercial production.

A major uncertainty affecting the feasibility of New Zealand farms as biopharms is the impact of horizontal gene transfer (HGT; see section 3.2.3). First, were HGT to be recognised as a significant risk of biopharming (in general or in relation to particular compounds), containment would become much more complex, to the point where it would likely require indoor facilities. This would add very significantly to the costs of the operation. One of the key actors we interviewed suggested that hygiene and purity demands for pharmaceuticals would require indoor production in any case, and that this would seriously undermine the economic feasibility of animal biopharming in New Zealand. A second major impact would be the limitations that would need to be placed on future uses of the land. The lack of flexibility in land use or sale implied by this was a major concern to our interviewees; few would be interested in embarking on an operation from which it would be practically impossible to opt out.

Even if certain types of animal biopharming are found by New Zealand regulators to be safe, and hence requiring minimal controls, overseas markets may force strict procedural standards regardless. This could mean, for example, that non-biopharm dairy farmers in New Zealand are required to perform additional procedures or tests in order to ensure access to key export markets.

6.2.3. Biopharm factories in New Zealand (Scenario 4)

From a number of perspectives, including hygiene and animal-health requirements of pharmaceutical regulators as well as issues raised by horizontal gene transfer, it could be argued that Scenario 4 (the self-contained, integrated biopharm) may be the most plausible. In this scenario, the operation produces its own animals in its research facility, farms them to produce transgenic milk, and processes the milk to extract the compound. This raises a number of questions regarding biopharming's benefits to New Zealand.

First, if it were to be seen as necessary to keep the biopharm animals indoors all or most of the time (as is the case with GTC Biotherapeutics' goats), this would appear to erode the potential cost-effectiveness of biopharming, particularly if using cows.

Second, there is the question of who could carry out such an operation. The most likely New Zealand candidate currently would be AgResearch or an AgResearch spin-off company. However, our interviewees at AgResearch were insistent that the point of developing the technology was for it to go out to New Zealand farmers. The array of highly technical skills and access to intellectual property needed to run this kind of self-contained operation, however, would appear to rule that out. It may be possible for Fonterra to embark on such an operation; however, our interviews suggested that Fonterra's own explorations of biopharming's potential had not produced a convincing economic case for this.

Third, if this model were to require investment and management by an overseas pharmaceutical or biotechnology company, there is reason to question whether it would happen in New Zealand at all. New Zealand's disease-free status could effectively be exported through the export of founder animals. Examples exist already of the use of stock sourced in New Zealand for this reason: Dolly, the first cloned sheep, was produced from a New Zealand sheep, and GTC's biopharm goat herd was produced from goats imported from New Zealand. This raises the question of why an overseas company would establish an operation of this kind in New Zealand when New Zealand-sourced "safe" animals can be used anywhere in the world.

Fourth, the amount of economic benefit that New Zealand would derive from a self-contained, overseas-owned biopharm operation would have to be weighed again the risks it may pose for New Zealand's primary-production exports (see Kaye-Blake et al., 2007).

6.3. Some preliminary findings of implications for risk assessment and risk management

Our interviews pointed to a number of factors that may not, under current approaches, be considered in risk assessment processes: the effects of ownership and personal assessments of risk on rule-following; the availability of competent staff and the ubiquity of human error; and the impact of economic incentives to flout rules.

6.3.1. Will controls be implemented?

Our interviews strongly suggest that it is relevant when assessing the risks of a proposed activity to consider whether it is practical to assume that mandated controls will be consistently implemented. Interviews with those with detailed knowledge of the relevant social contexts suggest that ownership arrangements as well as operators' and employees' personal assessments of and attitudes toward the risks involved may have a direct bearing on whether rules to minimise risks are followed.

6.3.2. Human error and expecting the unexpected

Most of the farmers assumed that human error is inevitable. They generally accepted that the natural environment and human behaviour cannot be completely controlled. From the interviewees' perspective it is not controversial to state that unexpected events and behaviour occur. Risk assessment should also work from this assumption.

A similar point is made by Marvier and Acker who list several examples of human error in the containment of corn to suggest that risk assessment should include the inevitability of human error (Marvier and Acker, 2005: 101). If, as they suggest, "smart, highly trained, and conscientious people make mistakes, and those mistakes may be repeated and go unnoticed for years" (Marvier and Acker 2005, p.102), it would seem advisable for risk assessors to consider systematically the implications of human error.

It may therefore be relevant to take into account the likelihood of an operation hiring well-qualified staff. In a tight labour market, farmers or biopharm companies may not be able to find staff that can be relied upon to understand and implement detailed controls. There may be little incentive for staff to gain skills particular to a biopharming operation that will not be saleable elsewhere. In a situation of staff shortages there may also just be too much work to do in a given time, making "short cuts" more likely. Alternatively, operators may be reluctant to pay the added costs of well-qualified labour in a "sellers' market". All of this suggests that risk assessment and management may require a more detailed understanding of labour needs and supply and/or more intensive monitoring of operations.

6.3.3. Taking account of economic influences in risk assessment

The findings regarding economic influences on farmer behaviour may have implications for how risk is assessed. Instead of treating the economic dimensions of a proposed activity or organism as a separate issue, quantifiable in terms of economic cost and benefit, it may be pertinent to view economic issues as integral to environmental and health risks. The farmers' comments illustrate that economic factors may influence behaviour relevant to such risks, such as the ability or willingness to follow safety prescriptions.

6.3.4. Legal protections and expectations of those potentially at risk

Finally, we note that interviewees expected that the Resource Management Act (RMA) would protect them from any potential negative impacts of a neighbouring biopharm.

> We are covered by the RMA anyway. Because [with the RMA], I wouldn't be allowed downstream effects, it shouldn't have [an] effect on me. The Resource Management Act will protect you there, because there has got to be tolerable land use.

However, the degree to which residents are protected by the RMA is unclear, as is the ability of local government to use the RMA to ensure stricter standards of containment than ERMA has imposed. While the courts have ruled the precautionary principle to be

inherent in the RMA, ERMA's use of the precautionary principle is optional (Terry, 2004: 17). Terry suggests that the government has not yet explored the implications of these conflicting standards of precaution (ibid.: v).

The potential for conflict between local government and ERMA rulings is also discussed by the Ministry for the Environment (MfE), which suggests that whilst it is possible for local governments to use the RMA to control the use of genetic modification (which would include biopharming) in their region, this would be very difficult to do. The Ministry's website states that the issues surrounding GM safety are "highly technical, meaning that councils are unlikely to have the skills to deal with these issues" (MfE, n.d.). As ERMA is a specialised body designated to perform risk analysis, MfE suggests it will be difficult for local governments to offer any legitimate reasons for GM not to proceed if approved by ERMA.

In our view, the findings from our interviews challenge this assumption. The interviews have shown that people who are unlikely to participate in ERMA's risk-assessment processes may have detailed knowledge of how animal biopharming could affect their particular local environment. Two conclusions may be drawn from this. One is that local authorities may, in some cases, have better access to this knowledge of the land and social practices within a region than would ERMA. Another is that processes for eliciting and utilising this knowledge would be a valuable addition to ERMA's repertoire.

References

Al-Kaff, N. S., Kreike, M. M., Covey, S. N., Pitcher, R., Page, A. M. & Dale, P. J. (2000). Plants rendered herbicide-susceptible by cauliflower mosaic virus-elicited suppression of a 35S promoter-regulated transgene. *Nature Biotechnology* 18: 995-999.

AgResearch. (2000). *Transgenic sheep (Ovis aries).* http://www.agresearch.co.nz/scied/search/biotech/print_gene_gmocasesheep1.htm. Accessed: 25/02/2006

Andrew, K. (2004). Court rejects sheep review. In *Dominion Post.* (Accessed on 07/04/2005 from Factiva database).

Angers, R. C., Browning, S. R., Seward, T. S., Sigurdson, C. J., Miller, M. W., Hoover, E. A. & Telling, G. C. (2006). Prions in skeletal muscles of deer with chronic wasting disease. *Science* 311: 1117.

Atkinson, K. (2005). *Erma says AgResearch can't make GE herd.* http://www.stuff.co.nz/stuff/0,2106,3483539a3600,00.html Accessed: 20/11/2005 .

Baguisi, Alexander, Behboodi, Esmail, Melican, David T., Pollock, Julie S., Destrempes, Margaret M., Cammuso, Christine, Williams, Jennifer L., Nims, Scott D., Porter, Catherine A., Midura, Patricia, Palacios, Monica J., Ayres, Sandra L., Denniston, Richard S., Hayes, Michael L., Ziomek, Carol A., Meade, Harry M., Godke, Robert A., Gavin, William G., Overström, Eric W. & Echelard, Yann. (1999). Production of goats by somatic cell nuclear transfer. *Nature Biotechnology* 17: 456 – 461.

Bardor, M., Faye, L. and Lerouge, P. (1999). Analysis of the N-glycosylation of recombinant glycoproteins produced in transgenic plants. Trends Pl. Sci. *4*, 376-380.

Baum, J. A., Bogaert, T., Clinton, W., Heck, G. R., Feldmann, P., Ilagan, O., Johnson, S., Plaetinck, G., Munyikwa, T., Pleau, M., et al. (2007). Control of coleopteran insect pests through RNA interference. *Nature Biotechnology* 25, 1322-1326.

Bayel, A.C.D. (2004). Animal use in biotechnology: issues and options – a New Zealand perspective. *ATLA* 32 (1): 377-381.

Beckman, R. J. & Goldberg, A. R. (2003). *Bold steps, new horizons: an external view of NZ biotech and its future in the global arena.* The Channel Group.

Bennett, David. (2006). Questions abound as rice industry faces GMO concerns. *Delta Farm Press* Aug 30 2006. http://www.printthis.clickability.com/pt/cpt?action=cpt&title=Quations+abound+as+rice. Accessed: 08/10/2007

Bhullar, S., Chakravarthy, S., Advani, S., Datta, S., Pental, D. & Burma, P. K. (2003). Strategies for development of functionally equivalent promoters with minimum sequence homology for transgene expression in plants: Cis-elements in a novel DNA context versus domain swapping. *Plant Physiology* 132(3): 988–998.

Bialy, Harvey. (1991). Transgenic pharming comes of age. *Bio/technology* 9: 786-787.

Bourdieu, Pierre. (1990[1980]). *The logic of practice.* (Trans. Richard Nice.) Cambridge: Polity Press.

Bucciantini, M., Giannoni, E., Chiti, F., Baroni, F., Formigli, L., Zurdo, J., Taddei, N., Ramoni, G., Dobson, C. M. & Stefani, M. (2002). Inherent toxicity of aggregates implies a common mechanism for protein misfolding diseases. *Nature* 416: 507-511.

Busch, L. and Bain, C. (2004). 'New! Improved? The Transformation of the Global Agrifood System', *Rural Sociology* 69: 321-346.

Business Wire. (2004). Protein-centric drug development and functional glycomics enrich biopharmaceuticals pipeline. Business Wire, New York, April 28, 2004, page 1.

Cambridge scientist reviews origins of BSE. (2001). http://www.admin.cam.ac.uk/news/dp/2001072701 Accessed: 15/12/2005 .

Campbell, A. M. (1998). Prions as examples of epigenetic inheritance. *ASM News* 64: 314-315.

Clark, John & Whitelaw, Bruce. (2003). A future for transgenic livestock. *Nature Reviews/Genetics* 4: 825-833.

Cogoni, C. & Macino, G. (2000). Post-transcriptional gene silencing across kingdoms. *Current Opinion in Genetics and Development* 10: 638-643.

Court told decision on GE trial site a concern for new landowner. (2004). http://www.rsnz.org/news/index.php?view=searchdate&year=2004&month=12&day=02. Accessed: 24/02/2006

Cow produced Lactoferrin Completes GRAS notification. (2006). http://www.checkbiotech.org/root/index.cfm?fuseaction=search&search=GRAS&doc_id=11963&start=1&fullsearch=0. Accessed: 24/02/2006

Dabrowska, K., Switala-Jelen, K., Opolski, A., Weber-Dabrowska, B. and Gorski, A. (2004). Bacteriophage penetration in vertebrates. J. Appl. Microbiol. *98*, 7-13.

de la Cruz, F. & Davies, J. (2000). Horizontal gene transfer and the origin of species: lessons from bacteria. *Trends in Microbiology* 8(3): 128-133.

Doolittle, W. F. (1999). Phylogenetic classification and the universal tree (taxonomies based on molecular sequences). *Science* 284: 2124-2130.

Dove, Alan. (2000). Milking the genome for profit. *Nature Biotechnology* 18: 1045-1048).

Dove, Alan. (2002). Uncorking the biomanufacturing bottleneck. *Nature Biotechnology* 20: 777- 779.

Dunning Hotopp, Julie C., Clark, Michael E., et al. (2007). Widespread lateral gene transfer from intracellular bacteria to multicellular eukaryotes. *Science* 21 September 2007:Vol. 317. no. 5845, pp. 1753-1756

Dyck, Michael K., Lacroix, Dan, Pothier, François & Sirard, Marc-André. (2003). Making recombinant proteins in animals – different systems, different applications. *TRENDS in Biotechnology* 27(9): 394-399.

Earle, Nikki & King, Graeme. (2007). *Report on the 6th APEC High Level Policy Dialogue on Agricultural Biotechnology*. 19-21 January 2007, Canberra, Australia. MAF.

Echelard,Y., Ziomek, C.A. & Meade, H.M. (2006). Production of recombinant therapeutic proteins in the milk of transgenic animals. *BioPharm International* 19: 36-46.

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

Ellis, R. J. and Pinheiro, J. T. (2002). Danger - misfolding proteins. Nature *416*, 483-484.

EMEA. (2007). *European Public Assessment Report (EPAR): Omnitrope: EPAR Summary for the public*. http://www.emea.europa.eu/humandocs/PDFs/EPAR/Omnitrope/060706en1.pdf Accessed: 26/09/2007

ERMA [Environmental Risk Management Authority]. (2001). *Environmental Risk Management Authority Decision/Control GMF98009 (Part II)*. http://www.ermanz.govt.nz/search/registers.html?id=132 Accessed: 02/08/2007 .

_____ (2002). Environmental Risk Management Authority Decision/Control GMD02028. http://www.ermanz.govt.nz/search/registers.html?id=6574. Accessed: 02/08/1007

_____. (2005). Assessment of economic risks, costs and benefits: consideration of impacts on the market economy. http://www.ermanz.govt.nz/resources/publications/pdfs/ER-TG-06-01.pdf Accessed: 23/02/2006

_____. (2007). ERMA New Zealand Evaluation and Review Report: Application for approval to field test in containment any genetically modified organisms. Application Code: GMF06001. To assess the agronomic performance, in the Lincoln region, over 10 years of vegetable and forage brassicas, specifically cabbage, broccoli, cauliflower and kale, modified for resistance to caterpillar pests like cabbage white butterfly and diamond-back moth. Sections 5.9.14 and 7.6. Available from www.erma.govt.nz.

_____. 2007a. Application by AgResearch for amendment of GMD02028 under Section 67A of the Hazardous Substances and New Organisms Act 1996 (GMD02028-008).

_____. (n.d.). ERMA record of amendments to approvals GMD02028 and GMF09009 (Part I). http://www.ermanz.govt.nz/appfiles/execsumm/pdf/GMD02028-006.pdf. Accessed: 02/08/2007

Etches, Robert J. (2006). Response to Ivarie: Competitive bioreactor hens on the horizon. *TRENDS in Biotechnology* 24(3): 101-2.

Farm Futures staff. (2006). Farmers file class action suit against Bayer, Riceland Foods for unapproved biotech rice. *Farm Futures* 8/30/2006. http://www.farmfutures.com/ME2/Segments/NewsHeadlines/Ptir.asp?Module=News. Accessed: 08/10/2007

FDA. (2006) Agency Response Letter GRAS Notice No. GRN 000162.

_____. (2007). Animal cloning: a draft risk assessment 28/12/2007. http://www.fda.gov/cvm/CloneRiskAssessment.pdf Accessed: 10/09/2007 .

_____. (n.d., a) Food and Drug Administration Center for Drug Evaluation and Research approved drug products with Therapeutic Equivalence Evaluations, 27th Edition, http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm.

_____. (n.d., b) GRAS guide. http://www.cfsan.fda.gov/~dms/grasguid.html

FDA investigates improper disposal of bioengineered pigs. (2003). http://www.fda.gov/cvm/Mar-Apr03.htm#2153. Accessed: 09/03/2005

Fiester, Autumn. (2005). Ethical issues in animal cloning. *Perspectives in Biology and Medicine* 48(3): 328-343.

Food and Beverage Taskforce. (2006). *Smart food, cool beverage: New Zealand's future in the food and beverage sector.* http://www.nzte.govt.nz/common/files/fbtaskforce-finalreport.pdf Accessed: 03/11/2006 .

Fonterra Milk Supply. (n.d.). *Information and requirements for farmers producing Colostrum for supply.* Fonterra Co-operative Dairy Group Limited: Auckland, N.Z.

Fox, Jeffrey L. (2003). Puzzling industry response to ProdiGene fiasco. *Nature Biotechnology* 21 (1): 3-4.

FRST [Foundation for Research, Science and Technology]. (2005a). Production of biopharmaceutic proteins. *Research Abstract & Report Databases.* http://www.frst.govt.nz/Public/Reporting/abstracts/Report.cfm?docNumber=7. Accessed: 21/08/2007

_____. (2005b). Reprogramming cells into cloned animals. *Research Abstract & Report Databases.* http://www.frst.govt.nz/Public/Reporting/abstracts/Report.cfm?docNumber=2. Accessed: 21/08/2007

_____. (2006a). Healthy cloned and transgenic cattle. *Research Abstract & Report Databases.* http://www.frst.govt.nz/Public/Reporting/reports06/Report.cfm?Report=41 Accessed: 20/08/2007 .

_____. (2006b). Reprogramming cells into cloned animals. *Research Abstract & Report Databases.* http://www.frst.govt.nz/Public/Reporting/reports06/Report.cfm?Report=19. Accessed: 20/08/2007

_____. (2006c). Transgenic cattle producing valuable proteins. *Research Abstract & Report Databases.* http://www.frst.govt.nz/Public/Reporting/reports06/Report.cfm?Report=20. Accessed: 20/08/2007

_____. (n.d.). *New and Novel Products through Reproductive and Transgenic Technologies. Case Study.* http://www.frst.govt.nz/evaluation/downloads/CSExecsummary01/NewAndNovelProducts.cfm Accessed: 27/08/2007 .

Gavin, W.G. (2001). The future of transgenics. *Reg Affairs Focus* 6: 13-18.

GE Free NZ. 2004. *ERMA challenged over cavalier attitude to science: Background.* www.gefree.org.nz/press/o23052004.htm Accessed: 27/09/07

_____. (2005). *ERMA failing public by forging ahead with GE cows.* http://www.scoop.co.nz/stories/SC0511/S00040.htm Accessed: 28/02/2006

Gibbs, M. J. and Weiller, G. F. (1999). Evidence that a plant virus switched hosts to infect a vertebrate and then recombined with a vertebrate-infecting virus. Proc. Natl. Acad. Sci. USA *96*, 8022-8027.

Giddings, L. Val. (2006). Whither agbiotechnology? What will the agbiotech landscape look like in 20016? And what form will the 'doubly green' revolution take? *Nature Biotechnology* 24(3): 274-276.

Gogarten, J.P. & Townsend, J.P. (2005). Horizontal gene transfer, genome innovation and evolution. *Nature Reviews Microbiology* 3: 679-687.

Goldman, M. (2003). Processing challenges for transgenic milk products. *BioProcess International* 10: 60-63.

Gomord, V., Chamberlain, P., Jefferis, R. and Faye, L. (2005). Biopharmaceutical production in plants: problems, solutions and opportunities. *Trends in Biotechnology 23*, 559-565.

Gordon, K. H. J. and Waterhouse, P. M. (2007). RNAi for insect-proof plants. *Nature Biotechnology* 25, 1231-1232.

Gorski, A., Wazna, E., Dabrowska, B.-W., Dabrowska, K., Switala-Jelen, K. and Miedzybrodzki, R. (2006). Bacteriophage translocation. *FEMS Immunolofgy & Medical Microbiology 46*, 313-319.

GTC Biotherapeutics. (n.d. (1)). Questions by scientists. Accessed on 28/08/2007 from http://www.gtc-bio.com/science/questions.html.

Hale, Tim. (2006). *AgResearch Annual Field Test Report: Annual Report to ERMA New Zealand. 31 December 2006.* http://www.ermanz.govt.nz/no/compliance/AgResearchComplianceReport06.pdf Accessed: 02/08/2007

Hansen, H., Okeke, M.I., Nilssen, O. & Traavik, T. (2004). Recombinant viruses obtained from co-infection in vitro with a live vaccinia-vectored influenza vaccine and a naturally occurring cowpox virus display different plaque phenotypes and loss of the transgene. *Vaccine* 23: 499-506.

Harvey, A.J., Speksnijder, G., Baugh, L. R, Morris, J. A. & Ivarie, R. (2002). Expression of exogenous protein in the egg white of transgenic chickens. *Nature Biotechnology* 19: 396-399.

Heinemann, J. A. (1999). How antibiotics cause antibiotic resistance. *Drug Discovery Today* 4: 72-79.

_____. (2007). A typology of the effects of (trans)gene flow on the conservation and sustainable use of genetic resources. Background Study Paper No.35, *Commission on Genetic Resources for Food and Agriculture, United Nations*. ftp://ftp.fao.org/ag/cgrfa/bsp/bsp35e.pdf. Accessed: 30/07/2007

Heinemann, J. A., Ankenbauer, R. G. and Amábile-Cuevas, C. F. (2000). Do antibiotics maintain antibiotic resistance? *Drug Discovery Today 5*, 195-204.

Heinemann, J. A. and Traavik, T. (2004). Problems in monitoring horizontal gene transfer in field trials of transgenic plants. *Nature Biotechnology* 22: 1105-1109.

Herrera, S. (2004). Biogenerics standoff. *Nature Biotechnology* 22(11): 1343-1346.

Hirschler, Ben. (2005). EU agency hopes for first biogeneric drugs in 2005. In *RSNZ News*, Reuters 12/03/05. http://www.rsnz.org/news/print.php?view=57002. Accessed: 19/09/2007

Houck, M. A., Clark, J. B., Peterson, K. R. & Kidwell, M. G. (1991). Possible horizontal transfer of Drosophila genes by the mite Proctolaelaps regalis. *Science* 253: 1125–1128.

Houdebine, L.M. (1995). The production of pharmaceutical proteins from the milk of transgenic animals. *Reproduction Nutrition Developments* 35: 609-617.

_____. (2005). Use of transgenic animals to improve human health and animal production. *Reproduction of Domestic Animals* 40: 269-281.

Hunt, L.M. (2004a). The rise and fall of DDT in New Zealand. *New Zealand Sociology (Special Issue: Rural Sociology)* 19(2): 240-259.

_____. (2004b). Factors determining the public understanding of GM technologies. *AgBiotechNet: the online service for agricultural biotechnology*, 6 (August) ABN 128. http://www.agbiotechnet.com/reviews/Database/sept04/html/ABN128.htm. Accessed: 30/07/2007

Hunt, L.M., Fairweather, J.R. & Coyle, F.J. (2003). *Public understandings of biotechnology in New Zealand: factors affecting the acceptability of five selected biotechnologies in New Zealand.* Research Report 266, AERU, Lincoln University.

Irwin, A. (1995). *Citizen science: a study of people, expertise, and sustainable development.* Routledge: London, New York.

Ivarie, Robert. (2006). Competitive bioreactor hens on the horizon. *TRENDS in Biotechnology* 24(3): 99-101.

Johnson, C. J., Phillips, K. E., Schramm, P. T., McKenzie, D., Aiken, J. M. and Pedersen, J. A. (2006). Prions adhere to soil minerals and remain infectious. *PLoS Pathogens 2*: e32.

Kaye-Blake, W, Saunders, C and Ferguson, L. (2007). *Preliminary economic evaluation of biopharming in New Zealand.* Lincoln University. AERU Research Report March 2007.

Keefer, C.L. (2004). Production of biproducts through the use of transgenic animal models. *Animal Reproduction Science* 82-83: 5-12.

Keefer, C., Pommer, J. & Robl, J. (2007). *The role of transgenic livestock in the treatment of human disease: animal agriculture's future through biotechnology, Part 6*. Issue paper 35. May 2007. Council for Agricultural Science and Technology (CAST), Ames, Iowa.

Keyes, M. E. (1999). The prion challenge to the 'central dogma' of molecular biology, 1965-1991. *Studies in History and Philosophy of Biological and Biomedical Sciences* 30a: 1-19.

Kidwell, M. G. (1993). Lateral transfer in natural populations of eukaryotes. *Annual Review of Genetics* 27: 235-256.

Krauskopf, Lewis. (2006). US approves Omnitrope, a synthetic version of the human growth hormone, Genotropin. In *RSNZ News*, Reuters, 01/06/06. http://www.rsnz.org/news/print.php?view=63214 Accessed: 19/09/2007

Kues, W. A. & Niemann, H. (2004). The Contribution of farm animals to human health. *TRENDS in Biotechnology* 22(6).

Laible, G. & Wells, D.N. (2007). Recent advances and future options for New Zealand agriculture derived from animal cloning and transgenics. *New Zealand Journal of Agricultural Research* 50: 103-124.

Laible, G., Brophy, B., Knighton, D. and Wells, D. N. (2007). Compositional analysis of dairy products derived from clones and cloned transgenic cattle. *Theriogenology* 67: 166-177.

Lane, K. T. and Beese, L. S. (2006). Thematic review series: Lipid Posttranslational Modifications. Structural biology of protein farnesyltransferase and geranylgeranyltransferase type I. *Journal of Lipid Research* 47, 681-699.

Ledford, Heidi. (2006). The farmyard drugstore. *Nature* 443: 16-17, 7 September 2006.

L.E.K. Consulting. (2006). New Zealand Biotechnology Industry Growth Report. Commissioned by NZBio, MoRST, NZTE.

Life Science Weekly. (2007). Viragen; recent developments of Viragen detailed. *Life Science Weekly*, Atlanta, April 3, 2007, p.3728.

Lillico, S.G., Sherman, A., McGrew, M.J., Robertson, C.D. et al. (2007). Oviduct-specific expression of two therapeutic proteins in transgenic hens. *Proceedings of the National Academy of Sciences of the United States of America* 104(6): 1771.

Manzi, A. E., Norgard-Sumnicht, K., Argade, S., Marth, J. D., van Halbeek, H. and Varki, A. (2000). Exploring the glycan repertoire of genetically modified mice by isolation and profiling of the major glycan classes and nano-NMR analysis of glycan mixtures. *Glycobiology* 10, 669-689.

Mao, Y.-B., Cai, W.-J., Wang, J.-W., Hong, G.-J., Tao, X.-Y., Wang, L.-J., Huang, Y.-P. and Chen, X.-Y. (2007). Silencing a cotton bollworm P450 monooxygenase gene by plant-mediated RNAi impairs larval tolerance of gossypol. *Nature Biotechnology* 25, 1307-1313.

Marvier, M. and Van Acker, R. C. (2005). Can crop transgenes be kept on a leash? *Frontiers in Ecology and Environment* 3: 99-106.

Meat & Wool New Zealand. (2005). *Goat industry: an overview*. Meat & Wool New Zealand, pp.1-4.

MfE [Ministry for the Environment]. (n.d.). *Genetic modification (GM) and local government.* http://www.mfe.govt.nz/issues/organisms/regulation/local-government.html Accessed: 25/01/2006 .
Ministry of Research, Science and Technology (MoRST).

Miller, M. W., Williams, E. S., Hobbs, N. T. and Wolfe, L. L. (2004). Environmental sources of prion transmission in mule deer. *Emerging Infectious Diseases* 10, 1003-1006.

Mitra, N., Sinha, S., Ramya, T. N. C. and Surolia, A. (2006). N-linked oligosaccharides as outfitters for glycoprotein folding, form and function. *Trends in Biochemical Sciences 31*, 156-163.

MoRST [Ministry of Research, Science and Technology]. (2005). *Futurewatch.* Ministry of Research, Science and Technology.
_____. (2006). NZ's strengths: large animal biotechnologies.
http://www.morst.govt.nz/current-work/biotechnology/NZ-strengths/large-animals/ Accessed: 27/08/2007

Moses, Vivian. (2002). Agricultural biotechnology and the UK public. *TRENDS in Biotechnology* 20 (9): 402-404.

Nakhies, G., Loutit, M. & Rogne, S. (2003). A review of the capability of the Environmental Risk Management Authority (ERMA) relating to the risk management of new organisms. Prepared for the Minister for the Environment.

Nature Biotechnology. 2002. Going with the flow. *Nature Biotechnology* 20(6): 527

New Zealand Government. (2003). *Implement BioTaskforce's recommendations.* New Zealand Government Press *Release* September 18 2003.
http://www.scoop.co.nz/stories/PA0309/S00429.htm Accessed: 1/03/2006

Norregaard Jensen, O. (2004). Modification-specific proteomics: characterization of post-translational modifications by mass spectrometry. *Current Opinion in Chemical Biology* 8, 33-41

NZTE [New Zealand Trade and Enterprise]. (2005). *Biotechnology, agritech and natural products*: s*ector engagement strategy* 2005-2006. http://www.nzte.govt.nz/common/files/ses-biotechnology05.pdf Accessed: 03/03/2006

NZPA. (2003). Gene flock fate under review. In *New Zealand Herald*. http://www.nzherald.co.nz/topic/print.cfm?c_id=220&objectid=3509140. Accessed: 10/03/2006

_____. (2007) AgResearch pushes GE development. In *Gisborne Herald* , 15 December 2007. http://www.gisborneherald.co.nz /Default.aspx?s=3&s1=2&id=0847654d4f4e423ea7f19374e5c7c9d5. Accessed: 18/12/07.

O'Neill, G. (2007). Australia tackles bird flu using RNAi. *Nature Biotechnology* 25, 605-606.

Operator AgResearch Ruakura Farm Containment Facility. (2004). AgResearch Annual Field Test Report: Annual Report to ERMA New Zealand. 31 December 2004. http://www.ermanz.govt.nz/no/compliance/AgResearchComplianceReport04.pdf Accessed: 02/08/2007

_____. (2005). AgResearch Annual Field Test Report: Annual Report to ERMA New Zealand. 31 December 2005. http://www.ermanz.govt.nz/no/compliance /AgResearchComplianceReport05.pdf Accessed: 02/08/2007

Osborne, R. (2007). Companies jostle for lead in RNAi, despite uncertainties. *Nature Biotechnology* 25, 1191-1192.

Patton, D. 2006. Pharming takes step towards lactoferrin commercialisation. 1 June. http://www.nutraingredients.com/news/ng.asp?n=64905-pharming-lactoferrin. Accessed: 30/07/2007

Peterson, A. T., Carroll, D. S., Mills, J. N. and Johnson, K. M. (2004). Potential mammalian filovirus reservoirs. *Emerging Infectious Diseases* 10, 2073-2081.

PEW Initiative on Food and Biotechnology. (2004). Issues in the regulation of genetically engineered plants and animals. Accessed on 19/10/2007 from http://pewagbiotech.org/research/regulation/Regulation.pdf.

_____. (2005). A future for animal biotechnology? *Proceedings from a forum hosted by the University of Illinois at Urbana-Champaign Agricultural Genome Science and Public Policy Program and the PEW Initiative on Food and Biotechnology*. http://pewagbiotech.org/events/1205/proceedings.pdf Accessed: 19/10/2007

Pharming Group N.V. (2005). Pharming announces partnership with AgResearch for human lactoferrin: license for protein production technology granted to AgResearch. http://www.pharming.com/index.php?act=show&pg=160 Accessed: 26/02/2006

Pickrell, John. (2002). Scrambled drugs: transgenic chickens could lay golden eggs. *Science News Online* 161(14) April 6. http://www.sciencenews.org/articles/20020406/fob5.asp Accessed: 03/11/2006

Pollak, D. (2003). *Clean, green and genetically modified? GMOs and the future of New Zealand*. http://www.fulbright.org.nz/voices/axford/docs/pollakd.pdf Accessed: 10/032006

Powell, D. (2001). Future farming: milking it for what it's worth. In *Trademark* October/November, 2001: 14-17.

Prescott, V. E., Campbell, P. M., Moore, A., Mattes, J., Rothenberg, M. E., Foster, P. S., Higgins, T. J. V. and Hogan, S. P. (2005). Transgenic Expression of Bean alpha-Amylase Inhibitor in Peas Results in Altered Structure and Immunogenicity. *Journal of Agriculture and Food Chemistry* 53, 9023-9030.

Prusiner, S. B. (1998). Prions. *Proceedings of National Academy of Science USA* 95: 13363-13383.

Redherring. (2006). Q&A: GTC's Geoffry Cox. *Redherring*, 12 January, 2006. http://www.redherring.com/Home/1529/. Accessed:10/09/2007.

Romanova, J., Katinger, D., Ferko, B., Voglauer, R., Mochalova, L., Bovin, N., Lim, W., Katinger, H. and Egorov, A. (2003). Distinct host range of influenza h3n2 virus isolates in vero and mdck cells is determined by cell specific glycosylation pattern. *Virology* 307, 90-97.

Rosin, C., H. Campbell and L. Hunt. (2007a). 'Audit Me This! Orchard-Level Effects of the EurepGAP Audit System on New Zealand Kiwifruit Producers'. In Stringer, C. and Le Heron, R. (eds.) *Globalising Worlds: Geographical Perspectives on Old and New Value Chains*. Ashgate: Avebury.

Rosin, C. L. Hunt, H. Campbell and J. Fairweather (2007b). There are Audits, and There are Audits: Response of New Zealand Kiwifruit Orchardists to the Implementation of Supermarket Initiated Audit Schemes. ARGOS Research Report 07/06. University of Otago: New Zealand.

Rosin, C. L. Hunt, H. Campbell and J. Fairweather (2007c). Becoming the Audited: Response of New Zealand Sheep/Beef Farmers to the Introduction of Supermarket Initiated Audit Schemes. ARGOS Research Report 07/05: University of Otago: New Zealand.

Ross, C. A. and Poirier, M. A. (2005). What is the role of protein aggregation in neurodegeneration? *Nature Reviews Molecular Cell Biology* 6, 891-898.

Rudd, P. M. and Dwek, R. A. (1997). Glycosylation: heterogeneity and the 3D structure of proteins. *Critical Reviews in Biochemistry and Molecular Biololgy* 32, 1-100.

RSNZ News. (2003). Ireland takes on world in biotech sweepstakes. http://www.rsnz.org/news/print.php?view=46522 Accessed: 18/09/2007

_____. (2005). EU agency hopes for first biogeneric drugs in 2005. http://www.rsnz.org/news/print.php?view=57002 Accessed:19/09/2007

_____. (2006). Complex biogenerics seem inevitable, but distant. http://www.rsnz.org/news/print.php?view=61941 Accessed: 19/09/2007

_____. (2007a). Argentine cow clones to produce insulin in milk. http://www.rsnz.org/news/print.php?view=68308 Accessed: 25/10/2007 .

_____.(2007b). A global increase of 13 percent to 252 million acres in 2006 – ISAAA. Sourced from Reuters 19/01/07. http://www.rsnz.org/news Accessed: 10/09/2007

Rudolph, Natalie S. (1999). Biopharmaceutical production in transgenic livestock. *TIBTECH* 17: 367-374.

Saint-Jore-Dupas, Claude, Faye, Loïc and Gomord, Véronique. (2007). From planta to pharma with glycosylation in the toolbox. *Trends in Biotechnology* 25(7): 317-323.
Saunders, C., Allison, G., Wreford, A., & Emanuelsson, M. (2005). *Food markets:trade risks and trends.* Agricultural Research Group on Sustainability. http://www.argos.org.nz/pdf_files/Food_Markets-Trade_Risks_and_Trends.pdf. Accessed: 03/11/2006

Schmidt, S. (2006). Belated approval of first recombinant protein from animal. *Nature Biotechnology* 24(8): 877.

Schmitz, T. G., Schmitz, A. & Moss, C. B. (2005). The economic impact of Starlink corn. *Agribusiness,* 21(3): 391-407.

Scientists warn of DDT trap. (1999). In *Dairy Exporter*. http://www.netlink.de/gen/Zeitung/1999/990827.htm Accessed: 07/03/2006 .

Scott, C. L., Hartweck, L. M., de Jesus Perez, J., Chen, D., Garcia, J. A. and Olszewski, N. E. 2008. SECRET AGENT, an Arabidopsis thaliana O-GlcNAc transferase, modifies the Plum pox virus capsid protein. FEBS Lett. *In Press, Corrected Proof*

Shearle, G. (2002). *The reality of a career in the dairy industry: An employee's Perspective.* Kellogg Rural Leadership Course 2002.

Smyth, Stuart, Khachatourians, George G., and Phillips, W.B. (2002). Liabilities and economics of transgenic crops. *Nature Biotechnology* 20(6): 537-541.

Somers, Terri. (2007). Cheaper biotech drugs? *Knight Ridder Tribune Business News*. Washington. July 13, 2007: p.1.

Stape, Andrea L. (2006). Amgen, hospital settle dispute. *Knight Ridder Tribune Business News.* Washington: June 7, 2006, p.1.

Suttie, James. (2007). AgResearch's transgenic livestock programme (Letter to stakeholders). http://www.agresearch.co.nz/transgenic/. Accessed 10/12/07.

Swanepoel, R., Leman, P. A., Burt, F. J., Zachariades, N. A., Braack, L. E. O., Ksiazek, T. G., Rollin, P. E., Zaki, S. R. and Peters, C. J. (1996). Experimental inoculation of plants and animals with Ebola virus. *Emerging Infectious Diseases* 2, 321-325

Syvanen, M. & Kado, C. I. (eds). (2002). *Horizontal Gene Transfer* (2nd ed.). San Diego: Academic Press.

Takeuchi, Y., Patience, C., Magre, S., Weiss, R. A., Banerjee, P. T., Le Tissier, P. and Stoye, J. P. (1998). Host Range and Interference Studies of Three Classes of Pig Endogenous Retrovirus. *Journal of Virology* 72, 9986-9991.

Tartaglia, G. G., Pechmann, S., Dobson, C. M. & Vendruscolo, M. (2007). Life on the edge: a link between gene expression levels and aggregation rates of human proteins. *Trends in Biochemical Science* 32: 204-206.

Taylor, M. R. & Tick, S.T. (2000). *The Starlink Case: issues for the future*, paper for Resources for the Future and Pew Initiative on Food and Biotechnology. http://pewagbiotech.org/resources/issuebriefs/starlink/starlink.pdf. Accessed: 10/04/2006

Taylor, P. (2005) Pharming licenses lactoferrin production tech to NZ group. *Nutraingredients*. 30 June. http://www.nutraingredients.com/news/ng.asp?id=60993-pharming-agresearch-lactoferin. Accessed: 30/07/2007
     Accessed:

Terry, S. (2004). *Community management of GMOs: issues, options and partnership with Government.* Simon Terry Associates Ltd: Wellington, NZ.

Thiel, Karl A. (2004). Biomanufacturing, from bust to boom…to bubble? *Nature Biotechnology* 22(11): 1365-1372).

Thomson, A.J. & McWhir, J. (2004). Biomedical and agricultural applications of animal transgenics. *Molecular Biotechnology 27*: 231-244.

U.S. National Research Council Committee on Defining Science-based Concerns Associated with Products of Animal Biotechnology. (2002). *Animal biotechnology: science-based concerns.* National Academies Press: Washington, D.C.

Van den Steen, P., Rudd, P. M., Dwek, R. A. and Opdenakker, G. (1998). Concepts and Principles of O-Linked Glycosylation. *Critical Reviews in Biochemistry and Molecular Biology* 33, 151-208

Verderosa, Christina. (2006). County farmers irritated about genetic rice flap. *DeWitt Era-Enterprise.* http://www.dewitt-ee.com/articles/2006/08/30news/news01.txt Accessed: 08/10/2007 .

Wall R.J. et al. (1997). Transgenic dairy cattle: genetic engineering on a large scale. *Journal of Dairy Science* 80: 2213-2224.

Walsh, Gary. (in press). Biopharmaceuticals: recent approvals and likely directions. *Trends in Biotechnology*.

Weaver, S. (2003). Biosecurity and GMOs in NZ. *Protect* vol. Winter.

Weld, R. & Heinemann, J. A. (2002). Horizontal transfer of proteins between species: part of the big picture or just a genetic vignette? In *Horizontal Gene Transfer*, C. I. Kado, and M. Syvanen, eds. (London and San Diego: Academic Press), pp. 51-62.

Wheeler, Matthew B. (2007). Agricultural applications for transgenic livestock. *Trends in Biotechnology* 25(5): 204-210.

White, Stan. (2005). Strategic use of scrapie-free donor animals in an international regulatory environment concerned with the control of Transmissible Spongioform Encephalopathies (TSE). Business Briefing: Global Healthcare: Medical Device Manufacturing and Technology 2005. www.capralogics.com/ScrapieFreeGoats.htm Accessed: 20/08/2007

Wilusz, C. J., Wang, W. and Peltz, S. W. (2001). Curbing the nonsense: the activation and regulation of mRNA surveillance. Genes Dev. *15*, 2781-2785.

Wisner, R. (2005). The economics of pharmaceutical crops: potential benefits and risks for farmers and rural communities. *Union of Concerned Scientists*. http://www.ucsusa.org/food_and_environment/genetic_engineering/economics-of-pharmaceutical-crops.html. Accessed: 30/07/2007

Woolhouse, M. E. J., Taylor, L. H. and Haydon, D. T. (2001). Population Biology of Multihost Pathogens. *Science* 292, 1109-1112.

Wynne, B. (1996). Misunderstood misunderstandings: social identities and public uptake of science. In *Misunderstanding science? The public reconstruction of science and technology*, Irwin, A. & Wynne, B. (eds). Cambridge, U.K.: Cambridge University Press.

Wynne, B. (1988). Unruly technology: practical rules, impractical discourses and public understanding. *Social Studies of Science* 18: 147-167.

Zasloff, M. (2002). Antimicrobial peptides of multicellular organisms. *Nature* 415, 389-395.

Zhou, Y., Chan, J. H., Chan, A., Y,, Chaka, R. K. F., Wong, E. Y. L., Chye, M.-L., Peiris, J. S. M., Poon, L. L. M. and Lam, E. (2004). Transgenic plant-derived siRNAs can suppress propagation of influenza virus in mammalian cells. *FEBS Letters* 577, 345–350.