Novel GM Animal Technologies and their Governance

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1. Introduction

New scientific developments, such as molecular editing techniques (e.g. zinc finger nucleases) and enhanced ways of introducing modifications (e.g. lentiviruses), are leading to an increasingly extensive range of potential GM animal applications. Proponents of GM animal production argue that some of these applications should be integral to the development of new diagnostic techniques and drugs for human diseases, through the production in animals of novel replacement proteins, vaccines, research models and tissues for the treatment and prevention of human diseases (COGEM 2011). They also propose that GM livestock have the potential to contribute to improving the environment and human health, with consumption of fewer resources and reduced waste production (Murray and Maga 2011). GM developments could also improve the welfare of animals by reducing disease incidence and enhancing overall health and well-being, minimising the need for care intervention (Kleter 2010; Maga and Murray 2010).

From an extensive survey we have identified over thirty GM animal applications under development or already in the market around the world, although this is likely to be an underestimate as some developments may not have been published. These data should therefore be considered illustrative. Most GM animals are currently used for research, for example to study mechanisms of gene action and function, or to test or produce new therapeutic agents. Commercial applications of GM animals include use as bioreactors to produce recombinant pharmaceutical proteins in milk, for example ATryn® (for blood clotting) and Ruconest™ (Rhucin® in non-European territories) to reduce acute swelling (Houdebine 2009;Vàzquez-Salat 2012) and potential use in xenotransplantation (the transplantation of cells, tissue or organs from one species to another) (Niemann et al. 2009; Ekser et al. 2012). There are currently no known GM animal food products on the market, but a faster growing GM salmon (AquAdvantage®) has been under regulatory review in the US since 1993 (Van Eenennaam and Muir 2011). Other animals have been modified to increase their growth rates and improve the quality of animal products (Marshall et al. 2006; Hume et al. 2011) including reducing the level of human allergens such as β-lactoglobulin (Jabed et al. 2012).

Pigs with a reduced environmental footprint (Golovan et al. 2001) were developed in Canada (Enviropig^{TM}) and were proceeding through regulatory approvals, although work on this has now reportedly ceased (Pig Progress 2012). China is said to have a major agricultural GM program to make more animal-based food available (GAIN 2011) and scientists in Africa are aiming to produce GM cattle resistant to sleeping sickness (Noyes et al. 2011). In the UK, scientists are developing GM chickens resistant to avian influenza (Lyall et al. 2011). GM animals have also been used to produce spider silk for medical and defence purposes (Lazaris et al. 2002; Service 2002), but this process was reportedly replaced by production from cells in culture (COGEM 2011). Another application involves GM insects produced to reduce spread of malaria and dengue fever to humans (COGEM 2011). Applications predominantly restricted to laboratory use or for the pet market (fish with enhanced colour range (Pray 2008)) are not considered in this paper. This wide range of applications in a number of species represent a diversity of different contexts, both natural and social.

Food security concerns are arising from a combination of population growth, impacts of climate change on weather, and competition for scarce resources, including water and energy. Global aggregate food production is projected to increase 60% between 2005/7 and 2050 to meet demand (Alexandratos and Bruinsma 2012, p7). At the same time, agriculture will need to adapt to the impact of climate change and will likely be expected to contribute to reducing greenhouse gas emissions (Garnett 2009). Greater and more frequent threats from plant and animal diseases are expected as climate change allows the spread of vector-borne diseases into new areas (Tomley and Shirley 2009) and these will be allied to changes in consumption patterns - the world demand for meat and milk is projected to more than double by 2050 (FAO 2009). China already consumes more than 25 percent of all the meat produced worldwide (Subramanian 2012), having increased from 8 million tonnes in 1976 to 71 million tonnes in 2012 (now more than double that in the US). These trends are leading to calls for 'sustainable intensification' of agricultural production (Foresight. The Future of Food and Farming 2011). It has been argued that GM animals could contribute greatly to meeting these challenges (Fahrenkrug et al. 2010; Hume et al. 2011).

Over sixty percent of the GM animals that we have identified as potentially for commercial application have been developed to produce pharmaceutical proteins or to be disease resistant. This suggests that these two categories are currently the most commercially attractive propositions, possibly because they could be considered less controversial than other applications. Sixty five percent of the GM animal applications we identified appear to be at advanced research stages and 25% are either in the approval process or have been approved for commercialisation (mostly in the pharmaceutical sector) (Figure 1). However, it is too early in the development of this technology to predict where the greatest economic and societal benefits will arise and which currently attractive applications of GM animals will be superseded by new production processes or even better

products. Some sectors, such as the pharmaceutical sector, may prove to be less controversial and develop more readily.

This paper considers the new scientific techniques that are enabling the development of GM animals, particularly for food and agriculture-related purposes, and examines the relevant regulatory approaches adopted particularly in the European Union (EU). The nature of the regulatory framework will determine companies' and nations' ability to benefit from these new innovative approaches to animal production, and we explore the potential innovation-related impact of current regulatory choices. This paper builds on our interdisciplinary expertise over two decades of following the development of GM technologies and the regulation of biotechnologies, supplemented by an extensive literature review of current developments worldwide. We synthesise findings from multiple research projects involving prolonged interaction with over 20 informants in research, regulation and industry and participant observation in industrial and regulatory meetings.

2. Scientific developments in GM animal production

Scientific research to develop GM animals has been ongoing since the early 1980s and now a range of new more precise techniques is offering opportunities for easier, more cost-effective and efficient generation of GM animals. These techniques differ in their suitability for different animal species, their efficiency of transformation, and their implications for risk assessment.

As shown in Figure 2, methods for introducing a genetic modification have evolved from microinjection into an early embryo (Gordon et al. 1980; Palmiter et al. 1982), through modification of cells in culture for subsequent re-introduction into an early embryo, to using viral vectors (such as lentiviruses) to introduce modified genes into a large number of cells, either in culture or in an embryo. Molecular techniques to manipulate the genetic material itself have evolved from inserting single genes (usually in combination with marker genes to allow the introduced gene to be identified) to manipulating individual nucleotides.

The original method, the injection of DNA coding for a specific novel trait into the nucleus of a fertilised egg (Clark and Whitelaw 2003; Ittner and Gotz 2007), is technically difficult and inefficient and only around 1 per cent of the treated embryos result in live GM animals (Le Provost et al. 2009). The expression of the novel gene also varies significantly as the technique is not able to target introduction of the gene to a precise location in the genome, or to control the number of copies introduced (Dove 2000). Thus, whilst conventional micro-injection based methods are successful in generating transgenic animals, the search for more efficient and more accurately targeted approaches has continued (Park 2007).

Nuclear transfer technology (cloning) was developed to overcome some of the technical issues with micro-injection by genetically modifying cells in culture, identifying cells that had been successfully modified and using these to develop GM animals (Suk et al. 2007; Buck 2011). In 1997, the first GM animal was produced in this way (Schnieke et al. 1997) but this technique is technically demanding and costly in comparison to other approaches (CAST 2009). Nuclear transfer has changed the timing and location of genetic modification from the early embryo to cell culture, and allowed selection of cells only with successful genetic modifications to be used to produce the animal.

Dramatic improvements in the efficiency of GM animal production took place in the early 2000s based on developments in human gene therapy. The use of lentiviruses instead of micro-injection to deliver genetic material allowed manipulation of both cell cultures and well-developed chick embryos (McGrew et al. 2004). According to Novosleva et al. (2007) using the standard microinjection procedure, between 1-5% of injected eggs gave rise to a transgenic founder animal, whereas through the use of lentiviral vectors, over 30% of the injected eggs resulted in a transgenic founder animal. An alternative method used to introduce new genetic material, drawing on developments in human fertility treatment, particularly the use of intra-cytoplasmic sperm injection (ICSI), is GM sperm injected directly into the egg (Kaneko et al. 2005).

Molecular methods of manipulating genetic material have also improved substantially with the ability to suppress the expression of existing genes. Most notably, RNA-interference (RNAi) has been used to regulate or prevent the expression of a gene resulting in chickens that are unable to transmit avian influenza (Lyall et al. 2011) and a range of other opportunities (Clark and Whitelaw 2003).

Additional methods for targeting modifications to a specific location in the genome include, in combination with nuclear transfer, homologous recombination of the introduced DNA fragment in donor cells, usually involving a selection marker (Cappechi 1989). More recently the ability to 'edit' DNA using a range of synthetic enzymes (nucleases) that act as molecular 'scissors' has further improved the capabilities of genetic technologies: (i) zinc finger nucleases (ZFNs) with each zinc finger targeting specific nucleotide triplets; and (ii) a group of nucleases created from Transcription Activator-Like Effectors (TALENs) with each TALE targeting individual

nucleotides in specified locations in the genome (Durai et al. 2005; Geurts et al. 2009; DeFranceso 2011; Carlson et al. 2012). Both ZFNs and TALENs and an even more recent RNA system known as CRISP-Cas (Wang et al. 2013) cause user-specified breaks in the DNA, and as the break is repaired small mutations or other changes readily occur at the desired site, either resulting in deactivation of the gene, or allowing new genetic material to be added. For example, a pig model of human familial hypercholesterolemia, to investigate predisposition to heart attack at an early age, is being developed using TALENs to knock out the relevant gene (Carlson et al. 2012), currently achieving 10-20% success rates in editing the founder population (Whitelaw, unpublished data).

Where is development of GM animals being funded? There are few publicly available data on research expenditure in the commercial GM animal sector. In the public sector, the low level of funding to support the development of GM animals in some jurisdictions has been criticised (Fernandez and Schook 2005; COGEM, 2011) and the US, UK, Australia and New Zealand are alleged to have gradually reduced public funding for this technology. Where public funding in the US and EU is available, the main focus is said to be on the environmental safety of GM animals.

A different scenario is occurring in emerging economies where public statements suggest heavy investment in research and development on GM animals. Taking China as a case in point, GM technology is part of the government's vision for food security. The government is the primary investor, having developed an extensive research programme to improve disease resistance in animals, produce valuable compounds and increase productivity (GAIN 2011; Yang et al. 2011). Publicly funded research institutes or universities have developed, or are researching, GM animals, but no arising technologies are known to be in commercial production. The first applications are expected to reach the market in two years (Yang et al. 2011; Yang, 2003). For example, the Heilongjiang Fishery Institute of Chinese Academy of Fishery Science has developed GM carp using a growth hormone gene, reported to be under field trial, and Shanghai Genon Nio-engineering has developed GM goats that express either a human lactoferrin or a lysozyme gene. The former has been approved for an enlarged field trial and the latter is under restricted field trial (GAIN 2011). More recently, scientists in China have used somatic cell nuclear transfer to demonstrate improvements in milk yields from cattle (Yang et al. 2011). The Chinese government has also invested in large scale research institutions and complexes including China Medical City in Taizhou, a national high-tech pharmaceutical park that includes research and development on GM animals and the Institute for Animal Science, dedicated to the development of GM cattle (Fernandez and Schook 2005).

In summary, the new genetic techniques that have emerged since 2000 have the ability to modify animals more easily and precisely and in many cases more cheaply. The modifications produced are more nuanced in nature, with much higher success rates and the increased range of possibilities for manipulating the genome of animals has increased scientific and commercial interest with much more significant investment in emerging than in developed economies. Where development is slow compared to the potential, this is at least partly related to the current state of regulatory systems, as discussed in the next section.

3 Regulatory issues in GM animal development and commercialisation

Regulatory systems are among the most important influences in determining the course of technological innovation. This is true in terms of which products can be developed safely, the type and size of companies able to commercialise new technology, and which nations and regions are able to prosper based on locally generated knowledge (Mittra et al. 2011). Until 2008 there appeared to be no serious impetus behind regulatory initiatives related to GM animals, but the prospect of some applications being market-ready has since stimulated activity on safety assessments internationally.

3.1 The International Context

International trade in food products are subject to regulation in the context of the Cartagena Biosafety Protocol and the World Trade Organization (WTO) agreements. The Cartagena Biosafety Protocol applies to Living Modified Organisms, including GM animals, and is intended to protect biodiversity. International regulatory guidance on GM animals within the WTO is given under the Codex Alimentarius (2008) building on the regulatory precedent of GM plants and microorganisms. In many cases it will not be appropriate to translate a regulatory approach developed for a different set of organisms directly across to GM animals. For example, the introduced DNA and/or derived products may impact either positively or negatively on the health status of the animals. GM animals may have either a greater or a lesser tendency to accumulate specific toxic substances or zoonotic pathogens that could be transmitted to consumers. This variability in potential impact leads to recommendations for a case-by-case approach to the regulation of GM animals, although the presumption in the EU has so far invariably been that this will be based on the systems currently in place for GM plants and micro-organisms.

Regulations are in place for GM animals in the USA (FDA 2009), Canada (Health Canada 2011) and Australia (AFAA 2004). In India a bill has been drafted to create the Biotechnology Regulatory Authority to be responsible for assessing all GM animal related applications (Vàzquez-Salat et al. 2010). Argentina has developed a case-by-case regulatory regime and was the first country in Latin America to develop two generations of GM cows capable of producing human growth hormone (Salamone 2006). Brazil also has introduced a Biosafety Law to regulate GM techniques (Mendon et al. 2008). As noted above, there are also strong emerging developments in China (Huang and Wang 2002; GAIN 2011).

One of the most important international issues in regulation of GM technologies continues to be differences in regulatory approaches focused primarily on the process by which new technology is developed, and those approaches focused primarily on the characteristics of the arising product. Europe (but not necessarily all its member states) is broadly seen as "process-based," Canada uses novelty as the regulatory trigger and is primarily "product-based," and the US is similarly product-based although technological process can have implications for deciding which regulatory pathway is appropriate. Although these differences emerged in the 1980s (Tait and Levidow 1992), they remain a source of international tension underlying, for example, US and EU trade disputes about GM crops that were heard by the WTO (WTO, 2010). Although there is a tendency to see the product-based approach as less antagonistic to innovation than the process-based approach, in practice both have their problems (Mandel 2004), and the differences between the approaches can be over-emphasised to make points about issues extending beyond the operations of regulatory authorities. Irrespective of whether a product or process-based approach is taken, there may be more fundamental presumptions to address first, namely the perception that GM animals raise more serious human risks than GM plants, and pose more significant environmental risks in light of their mobility and hence potential for invasiveness (Waigmann et al. 2012).

3.2 European Regulatory System

GM organisms used for food or feed in the EU are regulated through a centralised process governed by key legal instruments (EU Directive 2001/18/EC and Regulation (EC) 1829/2003). Processes for approval are built on a comparative approach that aims to identify biologically relevant differences by comparing the Genetically Modified Organism (GMO) with a non-GM counterpart. A GM animal may, however, need to be evaluated where there is no conventional counterpart. The European Food Safety Authority (EFSA) is the body charged with providing independent scientific advice to the European Parliament, European Commission and Member States on the basis of risk assessments related to food and feed safety, including risks related to the use of GMOs (plants, food animals and micro-organisms). In the case of GM animals, the relevant EFSA Guidance Document proposes the use of non-GM surrogates with similar characteristics, and the need for containment in the experimental environment. The Guidance Document will contain separate sections relevant to fish, insects and terrestrial mammals and birds, with case studies (Waigmann et al. 2012).

In 2011, to pre-empt marketing of food from GM animals before legislation was developed, the European Commission asked the EFSA to assess the possible risks for food and feed safety and for the environment, and also issues related to animal health and welfare (Bronzwaer 2008; EFSA 2012; EFSA 2013). As Vàzquez-Salat et al. (2010) note, disagreement persists over the application of EU GMO regulations at member state level, given that animal welfare is of higher political importance in some EU countries than in others. In the Netherlands and Denmark, GM animal regulation includes specific regulations on the ethical aspects of GM animal production. In the Netherlands, a political party with animal rights as their highest priority (The Party for the Animals) has parliamentary representation and national regulation includes the ethical principle that genetic modification of animals involves 'erosion of the species identity' and should only be permitted in the service of an application of substantial importance, e.g. medical uses but not food production (COGEM 2011). Apart from GM animals for pharmaceutical production, the regulatory regime in the EU remains untested with respect to other applications of GM animal technology.

There are several regulatory challenges in translating the EU GM crops regulatory approach to a system adapted to GM animals, such as the additional aspect of animal welfare, mobility and the status attributed to animals. As it stands, the existing GM crop regulation is itself under challenge due to developments in molecular biology which are pertinent to both crops and animals. For example, whereas GM animals produced by micro-injection or random insertion in nuclear transfer donor cells can be identified through the presence of the inserted gene construct with or without the presence of a marker gene, the same cannot be said for changes caused by genome 'editors'. In particular, TALENs and ZFNs may produce a change consisting of a single nucleotide, something that could be produced by a naturally occurring mutation and would therefore be difficult, if not impossible, to identify as artificially induced. The question remains whether these types of alterations would be classed as

genetic modifications under the definitions of the EU Directive (Dunwell, personal communication; Lusser and Davies 2013).

European governance of GM technologies, particularly where a product is likely to become part of a food chain, has been strongly influenced by political considerations, in which public opinion has tended to predominate over science-based risk assessment Vàzquez-Salat et al. (2012). Although the advice of the EFSA is scientifically based and may conclude that there are no significant risks associated with the use of a particular GMO, the political process into which this advice is injected has so far been able to prevent commercial application of the technology for GM crops. Policy makers operate on a presumption that European public reactions to GM crops will be negative and this is a major political consideration for several national governments with strong Green party representation, but may not fully reflect public attitudes as these can change with time (e.g. Gaskell et al. 2011). The intention to base regulatory systems for GM animals on the GM crop precedent could imply a continuing influence of political considerations rather than a decision process based on evidence of risks and benefits (Tait and Barker 2011; Vazquez-Salat and Houdebine 2013).

4 Regulation/Innovation Interactions

We have previously explored the nature of the relationships between innovation and regulation across a broad spectrum of life sciences (Milne and Tait 2009; Tait and Barker 2011; Mittra and Tait 2012; Mastroeni et al. 2013). We have demonstrated how regulation has implications not only for ensuring the safety and efficacy of the product being brought to market, but also for individual company strategies, for the type of firm that will be successful in bringing the products to market, and for the ability of an entire sector to contribute to national and regional economic development, as summarised in the following examples.

(i) The lengthy and costly regulatory system for drug development that has been built up over the past fifty years has generally favoured multinational companies (MNCs) in that it acted as a barrier to entry for new entrants, with the result that the sector is dominated by the innovation strategies of these MNCs (Tait et al. 2008; Mittra et al. 2011). Both regulators and industry increasingly recognise that this regulatory system is now so onerous that it is leading to failures in development of potentially safe and useful products and at least in the US ways are being sought to adapt the current regulatory systems to the opportunities presented by 21st century science (FDA 2011).

(ii) When new developments emerge in life sciences, the choice of regulatory approach, usually at an early stage in the development of practical innovations, will determine which products can eventually reach a market place and what scale of company will be needed to commercialise the technology. Only large multinational companies (MNCs) will be able to support the high levels of investment over long timescales required to commercialise most life science products, forcing all other innovators to work with the innovation strategies of the MNCs (Tait et al. 2008). Thus, the choice by the US Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) to develop the pharmaceutical regulatory system as the appropriate model for both cell therapies (Tait 2007; Mastroeni *et al.* 2012) and novel diagnostic technologies (Mittra and Tait 2012) is likely to mean that only large MNCs will be able to develop products in these areas, to the neglect of smaller niche market opportunities and of more innovative products and processes that would have arisen from a small and medium sized enterprise (SME) component of the sector.

(iii) Regulatory systems for GM crops provide another example of how an early choice of regulatory system will determine the future trajectory of a technology. In the 1980s, the choice of regulatory systems being considered for GM crops was between treating them as a new plant variety or as a new form of crop protection technology. The choice of the latter regulatory approach shifted the innovation trajectory from seed companies to agrochemical MNCs, with a different set of choices for first generation products, leading eventually to take-over of seed companies by the agrochemical MNCs and contributing to the negative public framing of the technology in Europe. For example, Monsanto embarked in the 1990s on a very expensive strategy of 'buying the route to market' (Chataway et al. 2004). The subsequent precautionary regulatory approach in Europe has failed to adapt to evidence of the safety and the benefits of these products and has led to a serious decline in innovation in GM crops directed to European agricultural systems (Tait 2008; Tait and Barker 2011).

As noted earlier sixty five percent of the GM animal applications identified in this review are at advanced research stages but companies do not seem to be pushing towards commercialisation (Figure 1). Potentially revolutionary scientific developments could create valuable opportunities in new innovative markets, but companies will be unwilling to invest in the new technologies while there is uncertainty about the nature of future markets, with the ambivalence of policymakers towards GM animal applications and with no clear regulatory path, Fernandez and Schook (2005 p6) observe:

> "…. between uncertain consumers and an unclear regulatory pathway, animal biotechnology finds itself at a crossroads. Will it simply stay where it is for the foreseeable future, idling but not progressing? Will it go forward to its logical destinations—such as agriculture and drug markets—or turn around and retreat the way it came, … a research tool that …. never ventures out to the farm or pharmaceutical factory? … will other countries developing animal biotechnology simply take the wheel and drive ahead, putting their own transgenic and cloned animal products on the market?"

In the absence of applications for commercial release in the EU, what can be learned from market authorisation processes in other jurisdictions? In an example of this process at work, in the late 1990s a line of GM pigs with the capability to digest plant phosphorus more efficiently, the Enviropig™, was developed at the University of Guelph, Canada, (Golovan et al. 2001). Enviropig™ reached the initial stages of the Canadian marketing authorisation procedure, but after more than a decade of interacting with regulators, in April 2012 Ontario Pork, one of the project's funders, decided to withdraw (Pig Progress, 2012). The Enviropig™ might have been the more elegant technological solution, but inorganic phosphate feed additives address the nutritional demands of pigs, whereas feed supplementation with phytase makes organic phosphate bioavailable and to an extent lessens phosphorus excretion. This illustrates the complex interactions between innovation and regulation: regulatory uncertainty made it impossible for the developer to assess the relative commercial advantage of the new technology, and the long time lag between proof-of-concept of the technology and approval for commercial applications introduced delays and uncertainties that made it unlikely that the modified pigs would be tested in the market.

A second example demonstrating the impact of regulatory delays and uncertainties on innovation is AquAdvantage® Salmon, being developed in the USA, that has been in a regulatory review process for over 15 years. The underlying brood stock are conventional farmed Atlantic salmon varieties, modified using pronuclear injection techniques, adding a growth hormone regulating gene from a Pacific Chinook salmon and a promoter from an ocean pout, to enable it to grow all year-round, instead of only during spring and summer. AquAdvantage® Salmon are claimed to reach market size twice as fast and to reach a mature size faster than traditional salmon without increasing in size, making them indistinguishable in appearance to conventional farmed salmon. Although they are bred to be sterile by pressure-induced triploidy, concerns about fish escapes have suggested to some that open water net pens should be replaced by either hard form floating containers, or on-land wholly contained facilities (Van Eeneennaam and Muir 2011).

When AquaBounty Technologies, the developer of AquAdvantage® Salmon, sought regulatory guidance from US Food and Drugs Administration (FDA) for its development and approval in 1993, no regulatory pathway existed for GM animals. The company petitioned for regulation under the FDA as they thought that this rigorous pathway for approval would help assuage public concerns regarding food from GM animals. AquaBounty Technologies submitted the first data set to the FDA in 1996 and 40 US Senators and Representatives wrote to the FDA requesting that it reject the application. The FDA continued to review the application to approve GM salmon or AquAdvantage® Salmon as the first genetically modified animal to be introduced into the United States food supply, and in September 2010 an FDA advisory panel indicated that the fish was generally safe (Van Eenennaam and Muir 2011). Since then high-level policy issues have further delayed formal approval of the modified salmon. In December 2012, the US FDA (2012) announced a preliminary finding that (p 5) "… an approval of this application … would not have a significant impact on the US environment". Subsequently, following a consultation period extended to April 26th 2013, final approval is still on hold in a process that has similarities with the interactions around scientific risk assessment by the EFSA and the politics of the European Parliament in the approval process for GM crops.

It is not unusual for the first applications of a novel technology to take a considerable time to obtain regulatory approval (for example Martineu (2001) traces the steps between 1990-94 to gain regulatory approval for one of the first GM crops, Calgene's Flavr Savr ™ tomato in the USA). It is also possible that these applications are considered more controversial than other applications. Nevertheless, time to market, combined with regulatory costs and uncertainties in the process, create serious challenges for technology developers that are likely to restrict the type of developer and the number of developers willing to invest in GM animal production. Difficulty in obtaining financial investment will particularly discourage smaller companies or public sector organisations, perhaps with more innovative applications, from entering these markets. Venture capitalists, in this as in other areas, tend to invest in technologies with clearer regulatory pathways to minimise costs, delays and uncertainties. By contrast, technologies that depend on breaking new regulatory ground can strand capital if they never reach the market, or if they do, they might be out-dated by the time they are approved. Most GM animals currently being developed in advanced economies are in university spin-off companies or small and medium enterprises that are unlikely to be able to negotiate a lengthy and costly regulatory process the outcome of which is uncertain.

Difficult regulatory environments in Europe and North America are thus likely to lead to research and development on GM animals moving to jurisdictions that are more favourable to development (COGEM 2001). For example, a project to manufacture anti-diarrhoea medicine from GM goats that express the human enzyme lysozyme in their milk (Murray et al. 2010), was transferred to Brazil in 2010 after 10 years of research in the US. Brazilian scientists have received $3.5 million from their government to initiate human trials of the goats' milk, whereas in the US the project received a $400,000 grant from US Department of Agriculture over three years for a study focused on the environmental safety of the GM animals. The decision to relocate the project was partly influenced both by the lack of funding and by the delay of more than 10 years by the US FDA in deciding how to regulate GM animals. The FDA issued guidance to those developing the product in January 2009 by which time they were already in discussions with colleagues in Brazil. Given successful human trials, the GM goat milk is expected to progress through the Brazilian approval process more smoothly and quickly than it would in the USA (Regaldo 2010).

Decisions on location of company activities are complex but the above instance seems likely to become a pattern unless clearer regulatory approaches with defined and evidence-based routes to market are developed in Europe and the US. In these regions regulatory regimes for GM animals produce, to varying degrees, a negative, reinforcing cycle of regulatory inertia, lack of investment, policy ambivalence, lack of research funding and lack of commercial products. Increasingly sophisticated and discriminating innovation in the methods available for producing GM animals raises questions about the current weak state of development of regulatory regimes in the EU and USA; about the appropriateness of regulations that have been derived in the context of previous generations of GM technology; and about the relevance of regulatory systems developed for GM crops and micro-organisms to GM animals. Furthermore, the international nature of life science innovation processes means that challenges to regulatory systems seen as inappropriate in the EU and USA could lead to major regional differences in the rate and scope of innovation in novel technologies and, potentially, to poor consideration of benefit, risk and safety issues.

5 A regulatory framework for GM animals

5.1 Innovation configurations as a basis for a regulatory framework

GM animals present complex and interacting problems for both innovators and regulators, in common with many other areas of life science innovation. The main problem with innovation-regulation interactions in the context of GM animals might lie in the apparent reluctance of policy-makers to engage in the development of regulations specific to GM animals. Falling back on GM crops as the appropriate regulatory precedent for GM animal developments might help to set part of the framework, but divergences in the regulation of conventional plants and animals already suggest that the differences between GM plant and animal regulation will outweigh the similarities. In addition, the technologies surveyed in this study suggest that caution needs to be exercised in using regulatory precepts and procedures developed for older technologies in the regulation of newer technologies. Given the small number of technologies for which commercial approval has been sought, it is unlikely that regulators will take the initiative. Yet to emerge is an integrated industry sector with the capacity to foster inter-organisational collaborations and a clear vision of the new, potentially path-breaking innovation portfolio it wants to develop a 'configuration of innovators' (Brown et al. 2001). This term 'configuration' captures the creation of a complex network of relationships among firms and between firms and key public constituencies. These can include the development of new institutional alignments, cultures, new 'social' markets and organisational resources. Although the Biotechnology Industry Organization and EuropaBio acts as advocates for industry, the concept, as described by Brown et al. 2001, extends beyond conglomerations of innovative companies.

The kind of configuration advocated by Brown et al. could greatly facilitate the development of effective GM animal regulatory systems. Indeed, given the diversity of types of GM animals and of areas of application of the technology, it is likely that there will be several such potential configurations, each requiring different regulatory approaches. Future regulatory frameworks for GM animals will need to take account of the dynamics of each set of configurational relationships given, as we note above, that the regulatory system adopted will determine the nature of the innovative products developed, their areas of application, and the time-scales for their development. Without a prior set of visions driving coherent programmes of innovation and contributing actively to the development of regulatory systems for GM animals, there is a strong probability that the emergent regulatory systems will not be responsive to either path-breaking or incremental innovation.

Innovation configurations that could build innovative momentum around animal bio-science developments could be based initially on the kinds of companies currently involved in producing the animals, as outlined below. These could then form the nuclei on which to build viable innovation configurations along with adaptive

regulatory approaches based on the markets for the products, and the risk and ethical issues raised by the innovations.

(i) Poultry, pigs and dairy cattle

The poultry and pig breeding sectors, and to some extent dairy cattle, are characterised by a high level of competition and a small number of dominant companies, with significant activity also from farmer co-operatives acting internationally. Where food uses are involved, food processing and distribution markets will be relevant. Individual farm businesses will also be key components of the value chain. Where there are health-related applications this may bring in large or small pharmaceutical companies either directly involved as breeders or as downstream processors and marketers of pharmaceutical products.

(ii) Beef cattle, sheep and goats

Breeding of animals in this sector in the EU is mainly in the hands of individual farmers or breeders or of farmer cooperatives, creating a challenge for the coordination activities required to bring together an effective innovation configuration. Depending on the type of innovation, the wider farming community will also need to be involved in downstream production as may food processors and distributors and also the health care sectors. This sector seems particularly unsuited for co-ordinating activities to promote development of GM animals.

(iii) Insects and fish

Insects and fish incorporating bioscience innovations are mainly produced by small and medium-sized Enterprises (SMEs). Without a well developed innovation configuration involving companies of a range of different sizes and influence, individual small companies in this area will struggle to be heard in debates about regulatory processes.

Configurations within each of these sub sectors depends on a number of actors perceiving a specific GM animal application as being advantageous to develop. As yet there is little evidence of such intentions in several of the sectors. Configurations built on each of these three subsectors will encounter different regulatory challenges depending on whether, for example: they are selling products into the food or pharmaceutical sector; the innovative developments they are working on are to improve the health, disease burden or productivity of the animals themselves or to improve the quality of animal products; and the extent to which the animals themselves may present environmental hazards (this last being particularly relevant to insects and fish).

5.2 Product and process based approaches

The above analysis creates a case for regulatory consideration of each animal bio-science related innovation primarily on the basis of the nature of the product itself, and secondarily on the process by which it was developed. As noted above, for EU jurisdiction, were the existing GM crop regulatory system adopted as the relevant precedent for animal-related developments, a process-based approach would be likely. A recent EFSA review of its risk assessment processes for GMOs (Waigmann et al. 2012 p6), suggests that process-based regulation is not inevitable, however. In the context of the 'product vs process' debate, it was remarked that "[g]iven the fast development of new breeding/production technologies applied to organisms, which may need a revision of current regulatory definitions of genetic modification, EFSA is prepared to investigate risk assessment strategies for modified organisms, based on the characteristics of obtained products rather than based on the applied breeding/production technology." If followed through, this could signal the beginning of a major shift in European regulatory systems as applied to GM and related technologies.

5.3 Regulating a diversity of technological innovation

Among the many functions of regulatory systems, a primary goal in the EU is reducing citizen exposure to hazards potentially posed by commercialised products and services. One view of regulation is that it serves innovators and the public best when it enables positive change in industry behaviour while carefully discriminating between types of risks that would be socially relevant (Mittra et al. 2011). Process-based regulations are indiscriminate when they apply equally to all GM organisms, irrespective of their properties, and product-based approaches do not discriminate among processes by which products are created. That much is tautological, but the salient point is that the principle goal of regulation is better met by considering the risks and benefits of product properties, for it is these that would be preferentially embraced or avoided by the public. Processes by which GM products are created are not benefits or risks in themselves.

One example of how discriminating, enabling regulation might be applied to GM animals is the development of chickens resistant to avian influenza. Award of provisional regulatory approval in a restricted range of highly monitored circumstances could provide opportunities to gather evidence of the effectiveness, management

requirements and any unexpected side effects of the chickens, in a range of commercial situations. Such data could be usefully collected in advance of any crisis such as an influenza pandemic. The high potential for human benefit could justify 'cautionary' use of the technology in a restricted range of circumstances.

In a second example, some might argue that genetic modifications deemed to be of welfare benefit could be given 'fast track' approval. Some beef cattle carry a natural genetic mutation and fail to develop horns (a state referred to as 'polled'). This genetic variant rarely occurs in dairy cattle. A lack of horns is advantageous in terms of human safety when handling the cattle and of reducing the potential for cattle to harm each other. Current practice is to prevent the development of horns using chemical, heat or other methods, but the polled state could be produced by inducing a genetic change in the relevant gene using TALENs (Ridley 2013). If it is accepted that such changes would be beneficial to both animal and human welfare, then a 'fast-track' approval approach could be adopted for this innovation.

Animal breeding activities currently are not subject to much regulation in the EU. Individual pedigree animals may be registered in herd books for quality assurance (the animal must be of the correct breed and have recognised parentage) or recorded in company databases. In many cases these records when combined with measurements on animals are essential for evaluation for genetic merit. Regulatory compliance tends to be restricted to those regulations pertaining to general agricultural practice such as animal welfare, environmental impact and animal disease control. Any regulatory process derived specifically for advanced biotechnology as applied to animals would require the current breeding industry to acquire new skills in regulatory compliance, but consideration should be given to which regulatory approaches would be most enabling of innovation.

Managing the transition from first generation GM animals to more mature techniques and applications of genetic manipulation could provide an opportunity for developing a more discriminating regulatory framework that might influence the direction of innovation in GM animals. Whether the case for using GM animals to support sustainable intensification is accepted or not, innovation in the field of GM animal technologies is arguably far ahead of the policy and regulatory environment. Future regulation of GM animals should be capable of evolving as scientific and technical capacity expands and as lessons are learned about the most appropriate forms of regulation. This requires flexibility in the face of uncertainties around the eventual applications, products, processes and risks of GM animals.

6 Conclusion

Specific GM animal regulatory frameworks are yet to be developed, and in the meantime other existing regulations, guidances and practices are being adapted in response to the few attempts to commercialise GM animal technology. Costs, delays and uncertainties are all but guaranteed, and for the foreseeable future one can expect a negative, reinforcing cycle of lack of commercial products, few regulatory changes, lack of investment, policy ambivalence and shortfalls in research funding where socio-economic impact is less assured. At the same time, innovation in the life sciences is reflected in increasingly sophisticated and discriminating methods of producing GM animals raising questions about the appropriateness of regulations derived on the basis of older technologies. Furthermore, the international nature of innovation means that challenges to restrictive regulations may derive from other jurisdictions. The time is ripe for re-examining GM animal regulation in the EU and elsewhere.

The lack of a network of organisations to provide impetus and vision for animal biotechnology innovation suggests that regulatory development is likely to be more difficult to achieve. Individual and groups of scientists have been effective in projecting visions of the future and individual companies have sought to realise some of these visions, but without a network of organisations providing an 'innovation configuration,' the absorptive capacity of the private sector remains untested.

Evidence from other industry sectors, such as pharmaceutical, medical diagnostic and GM crops suggests regulatory regimes are very influential in the type of companies able to commercialise new technologies, and the type of products they are able to market. Given the diversity in the technologies currently being developed, product-based approaches to the regulation of animal biotechnology are more appropriate.

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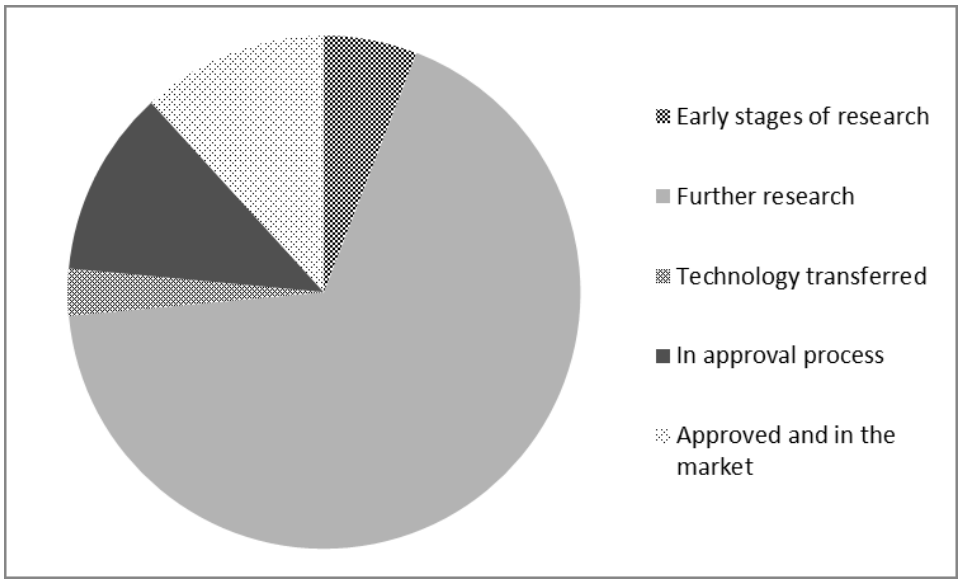

Figure 1. GM animals under development, in the pipeline or already in the market

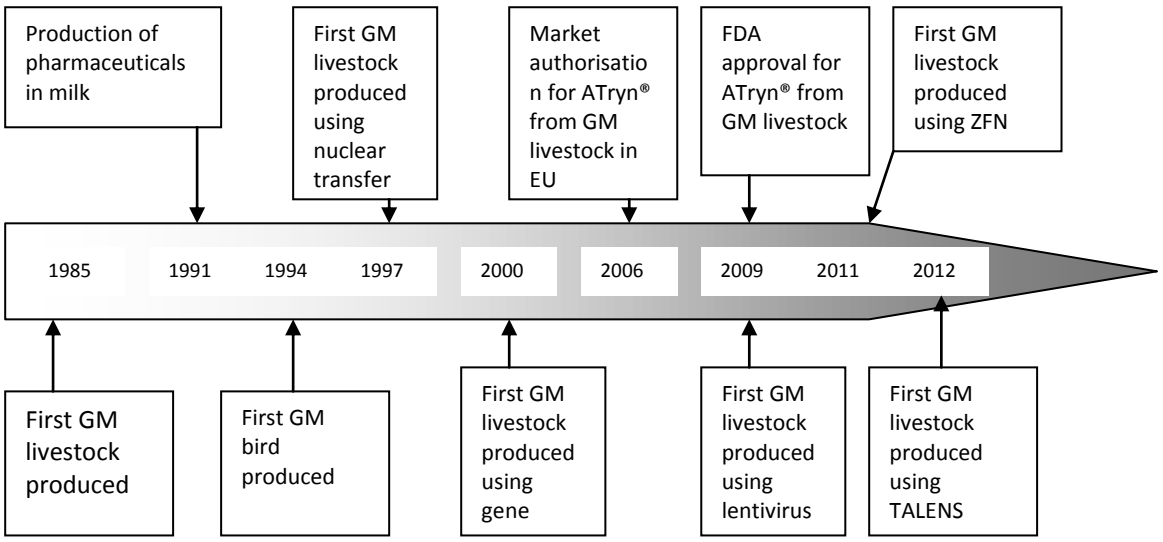

Figure 2. Emergence of new techniques for animal genetic modification

ZFN = Zinc finger nuclease
TALEN = Transcription Activator-Like Effector

References

AFAA (2004) Biotechnology and animal production. AgriFood Awareness Australia

Alexandratos N, Bruinsma, J (2012) World Agriculture Trends 2030/2050. The 2012 Revision. ESA working paper no. 12-03. Food and Agriculture Organization of the United Nations. http://www.fao.org/docrep/016/ap106e/ap106e.pdf. Accessed 27 May 2013

Bronzwaer S (2008) EFSA scientific forum 'from safe foods to healthy diets'. EU risk assessment – Past, present and future. Trends in Food Science and Technology 19:52-58

Brown N, Rappert B, Webster A, Cabello C, Sans-Menendez L, Markx F, van de Meulen B (2001) Final Report of the FORMAKIN Project, TSER Programme, Stage 2, Work Package 5/6, Jan, 2001. http://www.york.ac.uk/media/satsu/documents-papers/Brown-Rappert-2001-formakin.PDF. Accessed 9/4/13

Buck EH (2011) Genetically Engineered Fish and Seafood: Environmental Concerns. Congressional Research Service. Report for Congress

Capecchi, MR (1989) Altering the genome by homologous recombination. Science 244:1288-1292 PMID2660260

Carlson DF, Wenfang Tan, W, Lillico SG, Stverakovad D, Proudfoot C, Michelle Christiana M, Voytasa DF, Longf CR, Whitelaw CBA, Fahrenkrug, SC (2012) Efficient TALEN-mediated gene knockout in livestock. PNAS 109(43): 17382–17387

CAST (2009) Animal Productivity and Genetic Diversity. Part 8, IP43

Clark J, Whitelaw B (2003) A future for transgenic livestock. Nature Reviews 4:825-833

Chataway J, Tait J, Wield D (2004) Understanding company R&D strategies in agro-biotechnology: Trajectories and Blindspots. Research Policy, 33(6-7):1041-1057

Codex Alimentarius (2008) Guideline for the conduct of food safety assessment of foods derived from recombinant DNA animals. http://www.codexalimentarius.org/codex-home/en/. Accessed 4 April 2013

COGEM (2011) Genetically modified animals: a wanted and unwanted reality. COGEM Topic Report (CGM/120111-01) Independent scientific advice and information for the Dutch Government

DeFrancesco L (2011) Move over ZFNs. Nature Biotechnology 29 (7):681-684

Dove A (2000) Milking the genome for profit. Nature Biotechnology 18 (10):1045 – 1047

Durai S, Mani M, Kandavelou K, Wu J, Porteus MH, Chandrasegaran S (2005) Zinc finger nucleases: custom designed molecular scissors for genome engineering of plant and mammalian cells. Nucleic Acids Research 33 (18):5978-5990

EFSA Panels on GMO and AHAW (2012) Guidance on the risk assessment of food and feed from genetically modified animals and on animal health and welfare aspects. EFSA Journal 2012 10 (1): 2501 – 2544.

EFSA (2013) Guidance on the environmental risk assessment of genetically modified animals. EFSA Journal 11(5):3200
http://www.efsa.europa.eu/en/efsajournal/pub/3200.htm?utm_source=feedly. Accessed 25 May 2013

Ekser B, Edwin Klein E, Jing H, Stolz DB, Echeverri GJ, Long C, Lin CC, Mohamed E, Hidetaka H, Veroux M, Ayares D, Cooper DKC, Gridelli B (2012) Genetically Engineered Pig to Baboon Liver Xenotransplantation: Histopathology of Xenografts and Native Organs. PLoS One 7(1): e29720

Fahrenkrug SC, Blake A, Carlson DF, Doran T, Van Eenennaam A, Faber D, Galli C,Gao Q, Hackett PB, Li N, Maga EA, Muir WM, Murray, JD, Shi D, Stotish R, Sullivan E, Taylor JF, Walton M, Wheeler M, Whitelaw B,

Glenn BP (2010) Precision genetics for complex objectives in animal agriculture. Journal of Animal Science 88:2530-2539

FAO (2009) The state of food and agriculture – livestock in the balance. Food and Agriculture Orgainzation of the United Nations, Rome

FDA (2009) The Regulation of Genetically Engineered Animals containing Heritable Recombinant DNA constructs. Final Guidance

FDA (2011) Advancing Regulatory Science at FDA: a Strategic Plan. August 2011. http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm. Accessed 17 March 2013

FDA (2012) AquAdvantage Salmon Preliminary Finding. Prepared by the Center for Veterinary Medicine, United States Food and Drug Administration Department of Health and Human Services. 4 May 2012 http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/ucm280853.htm. Accessed 31 May 2013

Fernandez M, Schook L (2005) Introduction. In A Future for Animal Biotechnology. Proceedings from a forum hosted by the University of Illinois and the Pew Initiative on Food and Biotechnology, Chicago, Illinois, Dec. 2005, pp 5-6 http://www.pewtrusts.org/uploadedFiles/wwwpewtrustsorg/Summaries_-_reports_and_pubs/PIFB_Future_for_Animal_Biotech_Workshop_Proceedings.pdf. Accessed 17 March 2013

Foresight. The Future of Food and Farming (2011) Final Project Report. The Government Office for Science, London

GAIN (2011) China – People's Republic of, GE plants and animals. Annual 2010. GAIN report number CH11002. USDA Global Agricultural Information Network. http://gain.fas.usda.gov/Recent%20GAIN%20Publications/Biotechnology%20-%20GE%20Plants%20and%20Animals_Beijing_China%20-%20Peoples%20Republic%20of_3-15-2011.pdf. Accessed 31 May 2013

Garnett T (2009) Livestock-related greenhouse gas emissions: impacts and options for policy makers. Environmental Science & Policy 12:491-503

Gaskell G, Allansdottir A, Allum N, Castro P, Esmer Y, Fischler C, Jackson J, Kronberger N, Hampel J, Mejlgaard N, Quintanvilha A, Rammer A, Revuelta G, Stares S, Torgersen H, Wager W (2011) The 2010 Eurobarometer on the life sciences. Nature Biotechnology 29(2):113-114

Golovan SP, Meidinger RG, Ajakaiye A, Cottrill M, Wiederkehr M, Barney D, Plante C, Pollard J, Fan MZ, Hayes MA, Laursen J, Hjorth JP, Hacker RR, Phillips JP, Forsberg CW (2001) Pigs expressing salivary phytase and acid phosphatase activities. Can. J. Microbiology 46:59 – 71

Gordon JW, Scangos GA, Plotkin DJ, Barbosa JA, Ruddle FH (1980) Genetic transformation of mouse embryos by microinjection of purified DNA. Proc. Natl. Acad. Sci. USA 77:7380–7384

Geurts AM, Cost G.J, Freyvert Y, Zeitler B, Miller JC, Choi VM, Jenkins SS, Wood A (2009) Knockout Rats via Embryo Microinjection of Zinc-Finger Nucleases. Science 325 (5939): 433–433

Health Canada (2011) The Regulation of Genetically Modified food. http://www.hc-sc.gc.ca/sr-sr/pubs/biotech/reg_gen_mod-eng.php. Accessed 4 March 2013

Houdebine L-M (2009) Production of pharmaceutical proteins by transgenic animals. Comparative Immunology, Microbiology and Infectious Disease 32(2):107-121

Huang J, Wang Q (2002) Agricultural Biotechnology Development and Policy in China. AgBioForum 5(4):122-131

Hume DA, Whitelaw CBA, Archibald AL (2011) The future of animal production; improving productivity and sustainability. Journal of Agricultural Science 149: 9 – 16

Ittner LM, Gotz J (2007) Pronuclear injection for the production of transgenic mice. Nature Protocols 2: 1206 – 1215

Jabed A, Wagner S, McCraken J, Wells DW, Laible G (2012) Targeted microRNA expression in dairy cattle directs production of β-lactoglobulin-free high-casein milk. Proc. Nat. Acad. Sci. USA 109(42):16811-6

Kaneko T, Moisyadi S, Suganuma R, Hohn B, Yanagimachi R, Pelczar P (2005) Recombinase-mediated mouse transgenesis by intracytoplasmic sperm injection. Theriogenology 64:1704-15.

Kleter GA, Kok EJ (2010) Safety assessment of biotechnology used in animal production, including Genetically Modified (GM) feed and GM animals – a review. Animal Science Papers and Reports 28 (2):105 – 114

Lazaris A, Arcidiacono S, Huang Y, Zhou J-F, Duguay F, Chretien N, Welsh EA, Soareas W, Karatzas, CN (2002) Spider silk fibers spun from soluble recombinant silk produced in mammalian cells. Science 295: 472-476

Le Provost F, Lillico S, Passet B, Young R, Whitelaw B, Vilotte J-L (2009) Zinc finger nuclease technology heralds a new era in mammalian transgenesis. Trends in Biotechnology 28 (3):134-141

Lusser M, Davies HV (2013) Comparative regulatory approaches for groups of new plant breeding techniques. New Biotechnology (in press) http://dx.doi.org/10.1016/j.nbt.2013.02.004

Lyall J, Irvine RA, Sherman A, McKinley TJ, Nunez A, Purdie A, Outtrim L, Brown IH, Rolleston-Smith G, Sang H, Tiley L (2011) Suppression of Avian Influenza Transmission in Genetically Modified Chickens. Science 33: 223-226

Maga EA, Murray JD (2010) Welfare Applications of Genetically Engineered Animals for use in Agriculture. Journal of Animal Science 88:1588-1591

Mandel GN (2004) Gaps, inexperience, inconsistencies and overlaps: crisis in the regulation of genetically modified plants and animals. William and Mary Law Review 45:2167-2260

Marshall KM, Hurley WL, Shanks RD, Wheeler MB (2006) Effects of suckling intensity on milk yield and piglet growth from lactation-enhanced gilts. Journal of Animal Science 84:2346 – 2351

Martineau B (2001) First Fruit. The creation of the Flavr Savr™ tomato and the birth of biotech food. McGraw-Hill, New York

Mastroeni M, Tait J, Rosiello A (2013) Regional Innovation Policies in a Globally Connected Environment. Science and Public Policy 40(1):8-16

Mastroeni M, Mittra J, Tait J (2012) Methodology for the Analysis of Life Science Innovation Systems (ALSIS) and its Application to Three Case Studies. TSB Regenerative Medicine Programme: Value Systems and Business Models. REALISE Project. Innogen Centre Report to Technology Strategy Board. 29th May, 2012. http://www.genomicsnetwork.ac.uk/media/REALISE%20Case%20Study%20Report%20-%20Innogen.pdf. Accessed 4 April 2013

McGrew MJ, Sherman A, Ellard FM, Lillico SG, Gilhooley HJ, Kingsman AJ, Mitrophanous KA, Sang H (2004) Efficient production of germline transgenic chickens using lentiviral vectors. EMBO Reports 5:728-733

Mendon A-Hagler L, Souza L cia, Aleixo L cia, Oda L (2008) Trends in biotechnology and biosafety in Brazil. Environ. Biosafety Res. 7:115-121

Mittra J, Tait J, Wield D (2011) From maturity to value-added innovation: lessons from the pharmaceutical and agro-biotechnology industries. Trends in Biotechnology 29(3): 105-109

Milne CP, Tait J (2009) Evolution along the Government-Governance Continuum: FDA's Orphan Products and Fast Track Programs as Exemplars of "What Works" for Innovation and Regulation. Food and Drug Law Journal 64(4):733-753

Mittra, J, Tait J (2012) Analysing Stratified Medicine Business Models and Value Systems: Innovation-Regulation Interactions. New Biotechnology 29(6):709-719

Murray JD, Maga EA (2010) Is there a risk from not using GE animals? Transgenic Research 19:357-361

Murray JD, Mohamad-Fauzi N, Cooper CA, Maga EA (2010) Current status of transgenic animal research for human health applications. Acta Scientiae Veterinariae.38 (2) :627-632

Niemann H, Kues W, Carnwath JW (2009) Transgenic farm animals: present and future. Revue Scientifique et Technique 24:285 – 298

Noyes H, Brass A, Obara I, Anderson S, Archibald AL, Bradley DG, Fisher P, Freeman A, Gibson J, Gicheru M, Hall L, Hanotte O, Hulme H, McKeever D, Murray C, Oh SJ, Tate C, Smith K, Tapio M, Wambugo J, Williams DJ, Agaba M, Kemp SJ (2011) Genetic and expression analysis of cattle identifies candidate gene in pathways responding to Trypanosoma congolense infection. Proceedings of the National Academy of Sciences 108 (22):9304 – 9309

Novosleva TA, Meuwissen MPM, Huirne RBM (2007) Adoption of GM technology in livestock production chains: an integrating framework. Trends in Food Science and Technology 18:175-188

Palmiter RD, Brinster RL, Hammer RE, Trumbauer ME, Rosenfeld MG, Birnberg NC, Evans RM (1982) Dramatic growth of mice that develop from eggs microinjected with metallothionein-growth hormone fusion genes. Nature 300: 611-615

Park F (2007) Lentiviral vectors; are they the future of animal transgenesis? Physiological Genomics 31: 159-173

Pig Progress (2012) Enviropig project halted as Ontario Pork pulls the plug. http://www.pigprogress.net/Health-Diseases/Research/2012/4/Enviropig-project-halted-as-Ontario-Pork-pulls-the-plug-PP008578W/. Accessed 4 April 2012

Pray L (2008) Recombinant DNA technology and transgenic animals. Nature Education 1(1)

Regaldo A (2010) Building a Better Goat. MIT Technology Review. http://www.technologyreview.com/news/421268/building-a-better-goat/ . Accessed 10 March 2013

Ridley M (2013) Editing our Genes, One Letter at a Time. The Wall Street Journal, Mind and Matter. January 11th

Salamone D, Barañao L, Santos C, Bussmann L, Artuso J, Werning C, Prync A, Carbonetto C, Dabsys S, Munar C, Salaberry R, Berra G, Berra I, Fernández N, Papouchado M, Foti M, Judewicz N, Mujica I, Muñoz L, Alvarez SF, González E, Zimmermann J, Criscuolo M, Melo C (2006) High level expression of bioactive recombinant hormone growth hormone in the milk of transgenic cows. Journal of Biotechnology 124 (2):46 – 72

Schnieke AE, Kind AJ, Ritchie WA, Mycock K, Scott AR, Ritchie M, Wilmut I, Colman A, Campbell KH (1997) Human factor IX transgenic sheep produced by transfer of nuclei from transfected fetal fibroblasts. Science 278:2130-2133

Service F (2002) Mammalian cells spin a spidery new yarn. Science 295 (5554): 419-421

Subramanian V (2012) Driving forces in global agriculture. Rice Today – International Rice Research Institute. 11 (2):40-41

Suk J, Bruce A, Gertz R, Whitelaw CBA, Braun A, Oram C, Rodriguez-Cerezo E, Papatryfon I (2007). Dolly for dinner? assessing commercial and regulatory trends in cloned livestock. Nature Biotechnology 25(1):47-53

Tait J (2007) Systemic interactions in Life Science Innovation. Technology Analysis and Strategic Management 19 (3):257 – 277

Tait J (2008) Risk Governance of Genetically Modified Crops: European and American Perspectives. In: Renn O, Walker K (eds) Global Risk Governance: Concept and Practice Using the IRGC Framework. Dordrecht, NL: Springer Science and Business Media; pp 133-153

Tait J, Barker G (2011) Global food security and the governance of modern biotechnologies: opportunities and challenges for Europe. EMBO Reports 12:763-768

Tait J, Levidow L (1992) Proactive and reactive approaches to risk regulation: The case of biotechnology. Futures 24(3): 219-231

Tait J, with Wield D, Chataway J, Bruce A (2008) Health Biotechnology to 2030. Report to OECD International Futures Project, "The Bio-Economy to 2030: Designing a Policy Agenda", OECD, Paris, pp 51; http://www.oecd.org/dataoecd/12/10/40922867.pdf. Accessed 4 April 2013

Tomley FM, Shirley MW (2009) Livestock infectious diseases and zoonoses. Philosophical Transactions of the Royal Society B 364:2637-2642

Van Eenennaam AL, Muir WM (2011) Transgenic salmon: a final leap to the grocery shelf. Nature Biotechnology 29 (8):706-7011

Vàzquez-Salat N, Salter B, Smets G (2010) International Multi-level Governance of Genetically Modified Organisms: EU, USA and India. Work Package 6: Activity 6.1. *PEGASUS*

Vàzquez-Salat N, Houdebine LM (2013) Will GM animals follow the GM plant fate? Transgenic Research 22:5 – 13

Vàzquez-Salat N, Salter B, Smets G, Houdebine LM (2012) The current state of GMO governance: Are we ready for GM animals? Biotechnological Advances 30:1336-1343

Waigmann E, Paoletti C, Davies H, Perry J, Kärenlampi S, Kuiper H (2012) Risk assessment of Genetically Modified Organisms (GMOs). EFSA Journal 10(10) s1008:1-7
http://www.efsa.europa.eu/en/efsajournal/pub/s1008.htm . Accessed 31 May 2013

Wang H, Yang H, Shivalila CS, Dawlaty MM, Cheng AW, Zhang F, Jaenisch R (2013) One-Step Generation of Mice Carrying Mutations in Multiple Genes by CRISPR/Cas-Mediated Genome Engineering. Cell May 9;153(4):910-8

World Trade Organization (WTO) (2010) European Communities – Measures Affecting the Approval and Marketing of Biotech Products. http://www.wto.org/english/tratop_e/dispu_e/cases_e/ds291_e.htm. Accessed 27 May 2013

Yang,W (2003) Regulation of Genetically Modified Organisms in China. RECIEL 12 (1):99-108

Yang B, Wang J, Tang B, Liu Y, Guo C, Yang P, Yu T, Li R, Zhao J, Zhang L, Dai Y, Li N (2011) Characterisation of Bioactive Recombinant Human Lysozyme Expressed in Milk of Transgenic Cattle. PLoS ONE 6 (3):1-10