

Transgenic livestock: Regulation and science in a changing environment

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ABSTRACT: Regulatory policy for transgenic livestock is being developed concurrently with several rapidly advancing technologies for creating such animals. Adequacy of ethical, welfare, physiological, and environmental criteria applied to the selection of transgenes will have substantial implications for acceptance. Concurrent evolution of regulatory policy and oversight will determine whether the existing collaboration of animal drug, veterinary biologic, environmental, and food safety agencies is appropriate. Industry infrastructure

that interfaces with regulation, such as animal identification, genetic evaluation, diagnostics, and marketing practices, will also be challenged by transgenic innovation. Regulatory programs, especially those involved with diagnostics, laboratory analyses, trade in animals and animal products, and disease eradication will likewise require reassessment. Regulatory policy and industry practices associated with transgenic livestock, and the welfare, safety, and quality characteristics of these innovations, must be effectively communicated to achieve consumer acceptance.

Key Words: Food Safety, Genetics, Regulations, Transgenic Animals

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Introduction

Transgenic animals first emerged during the mid-1980s with the work of Palmiter et al. (1982). That work opened the way for applications of transgenesis in animals and has resulted in efforts along four lines: production of pharmaceuticals expressed in milk, production of animals as organ donors for xenotransplants, creation of models for study of human disease, and development of livestock suitable for use in agriculture.

This review will identify the key criteria, opportunities, constraints and concerns shared by consumers, industry, and regulators in the development of policy to guide the application of transgenesis in livestock agriculture. It will also indicate where and how the presence of transgenic animals in livestock populations would interface with current policy and regulations pertaining to agricultural livestock. Specific details of proprietary transgenic technology will not be addressed, nor will the details of specific agricultural applications in development. Rather, the purpose is to present a review of publicly available information and discuss the “scientific common sense” surrounding livestock transgenesis. Our purpose is to provide a background briefing and to stimulate dialogue among consumers, industry,

and regulators. Some of the regulatory implications for reproductive technology, including transgenic technology, have been reviewed recently (Evans, 1999).

Background of Current Regulatory Policy

Although it is still evolving, the regulatory pathway for transgenic livestock seems to be developing differently from the existing pathway for transgenic plants. Present federal policy is a consequence of the 1986 Domestic Policy Council “Coordinated Framework for the Regulation of Biotechnology,” which placed responsibility for regulation of biotechnology with several agencies, including the U.S. Food and Drug Administration (FDA), USDA, and U.S. Environmental Protection Agency (EPA). The agency responsible for regulatory oversight of each transgenic organism is determined by the nature and intended purpose of the transgene involved. At some institutions, transgenic animal research and development are subject to provisions of the Animal Welfare Act and the recombinant DNA requirements of the National Institutes of Health.

The present regulatory model for transgenic livestock in agriculture entails use of the New Animal Drug authority of FDA’s Center for Veterinary Medicine to evaluate safety and effectiveness of most transgenes (Matheson, 1999). This model may afford an opportunity for evaluation of process and product that could increase consumer confidence in the resulting food products. Obviously, regulation based on livestock genotype breaks new ground for the agencies involved. For the animal drug model to work, regulatory agencies

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and production agriculture need to consider its implications and to evaluate the capacity of the industry infrastructure needed to support effective regulation. Not all transgenic livestock will come under animal drug regulations, so significant interagency cooperation will be necessary.

The implications of product-specific oversight of transgenes become apparent from a few examples. Most transgenes affecting animal performance or function would fall under the authority of the FDA's Center for Veterinary Medicine (CVM). Transgenes producing constitutive immunity would be considered veterinary biologics, the responsibility of the USDA Animal and Plant Health Inspection Service (APHIS), Center for Veterinary Biologics. Transgene-mediated expression of a pesticide-like product is the responsibility of the EPA. Each of these agencies is responsible for interacting with food safety regulators, such as FDA's Center for Food Safety and Applied Nutrition, and USDA's Food Safety and Inspection Service.

The focus of this review is on agricultural applications in the United States, and its emphasis will be on transgenic applications in cattle, swine, and sheep. Where the term livestock is used, it should be interpreted as referring to these species. Technology for the production of transgenic poultry is less advanced (Wong et al., 1999).

Criteria for Use of Transgenes in Agricultural Livestock

What factors determine whether an approach to transgenesis is appropriate for agricultural use?

Utility: Benefit to Humans and Animals. The goal of gene transfer should be to enhance the quality of life for humans or the livestock being developed, or to significantly benefit resource conservation. Transgenesis offers the opportunity to increase performance of agricultural animals through improved feed intake, enhanced metabolism, better feed conversion, or reduced pathogen load; create novel or enhanced food and fiber products, permitting diversification of agricultural products; and reduce susceptibility to diseases, thereby improving food quality and security, decreasing antibiotic use, and enhancing resource conservation.

Safety, Ethical, and Welfare Considerations. Development of transgenic organisms is proceeding in an environment of intense public debate about safety, environmental impacts, and ethics of the technology. Some of the issues framed in this debate can be addressed through science, whereas others are inseparable from one's world view and ethical framework for decision making. Good science alone cannot ensure public acceptance of transgenic livestock animals, and both bad science and bad communication with society have the potential to severely damage and delay acceptance. Fundamental to good science and good public communication are openness to questioning and review not only by scientific peers, but also by the larger society. One

group has proposed the use of an "ethical matrix" intended to encompass the often divergent concerns of the scientific community and the public about transgenic animals (Mepham et al., 1998).

The technology employed for introduction of transgenes into a livestock population may produce consequences specific to the method. Once introduced, transgenic animals will become subject to the traditional selection criteria of livestock producers and the market forces for the gene products involved. A transgene will likely be expanded into the breeding population so long as the associated trait remains desirable in production systems and the marketplace. By use of marker-assisted selection, a few transgenes could be selectively incorporated into or eliminated from an otherwise diverse breeding population without great difficulty. On the other hand, if nuclear transfer technology becomes sufficiently efficient to enable it to contribute to livestock breeding, livestock breeders will then face critical long-term choices regarding the breadth of the genetic base. Would producers choose sexual (conventional breeding) or asexual (nuclear transfer) propagation of livestock? Would it become necessary to establish widespread germ plasm conservation for livestock, against such time that changing conditions make genotypes other than those widely adopted through asexual propagation necessary?

Genetic selection programs for livestock are also environmental choices. Genetic modifications, whether by traditional or transgenic methods, can change productivity in ways that may reduce the number of livestock that must be maintained, the amounts and characteristics of feedstuffs fed, the pharmaceuticals and pesticides used to maintain health, and the amount of animal waste that must be disposed. The utility of such modifications can be independent of the specific production system being employed or can be strongly linked to housing and nutritional management. Transgene-controlled modifications to animal digestion or metabolism that fundamentally change animals' capacity to utilize specific feed ingredients or forages, or that alter the composition of animal waste, would clearly have profound environmental consequences. As the growth of the human population continues to decrease the amount of arable cropland, choices made regarding the genotypes of the livestock being raised, and the associated production systems, will become increasingly critical.

Safety, Welfare, and Productivity. There is no better guide to those who create or regulate use of transgenic livestock than the injunction "first, do no harm." It is recognized that occasionally, unexpected detrimental effects of gene insertion will occur, and these effects will not be detected until after birth. In this context, several concerns regarding introduction of a transgene must be considered. Choice of the gene selected for transfer is the most controllable step to avoid adverse side effects. As shown from early experiments with transgenic swine, genes encoding proteins but lacking

physiologically relevant expression patterns may pose significant animal safety and welfare risks (Pursel et al., 1987).

In addition to concerns that encompass all uses of transgenic animal technology, some considerations for risk assessment are pertinent only to certain gene transfer methods. For example, use of replication-defective retrovectors for introducing transgenes into the food chain will be accompanied by the need to demonstrate the biological safety of the vector, notwithstanding the numerous endogenous and exogenous retroviruses already prevalent among domestic animals (Rosenberg et al., 1997). Development of transgenic and conventional farm animals using nuclear transfer technology has now produced several reports describing risks to the welfare of transgenic offspring and surrogate dams consequent to fetal oversize and perinatal mortality of dams and offspring (Hill et al., 1999; Kruijff et al., 1997).

Phenomena such as these highlight the relevance of ethical and animal welfare issues to transgenic livestock research and development. Peer and outside reviews of proposed transgenic animal research are embodied in the Institutional Animal Care and Use Committee (IACUC) overseeing entities regulated under the Animal Welfare Act (AWA). This approach should comprise an effective way to address such issues, provided the IACUC members are adequately informed about relevant technical and ethical concerns. Transgenic animal and associated reproductive technology research carried out by entities not subject to the AWA is not subject to obligatory scrutiny by IACUC. Whether such review should be applied more broadly is a policy option worthy of consideration by the relevant regulatory agencies.

Some of the welfare concerns relevant to evaluation of transgenic animal research and development proposals have been described:

Evaluation of proposals for the creation of transgenic animals may be divided into two interrelated parts: first, the justification for creation of the particular transgenic animal; and secondly, the welfare issues underlying the creation process itself. Special attention must be devoted to new protocols that use, for example, previously uncharacterized vectors or new transgenes, and/or are being performed by investigators who are new to the techniques (CCAC, 1997).

In considering the ethical and animal welfare implications of transgenic animal development, costs and benefits may need to be framed in the context of the intended use of the animals. For example, development of transgenic livestock intended to become founders of lines used for pharmaceutical production may possess sufficiently greater potential societal benefit, and thereby justify a different risk/benefit calculation, than would be the case for agricultural applications. Modern management practices and producer attitudes would

weigh heavily against any animals, transgenic or not, whose use would result in a significantly increased risk of pregnancy wastage, dystocia, fetal abnormalities, or neonatal losses.

Notwithstanding the genome's abundant non-coding regions, all gene transfer methods can potentially produce insertional mutagenesis of an essential host gene. It has been suggested that transgenic animals should be bred to achieve homozygosity of the transgene in order to demonstrate absence of such mutations (Mepham et al., 1998). Such evaluations could be accomplished quickly in an inbred species having a short generation interval. However, in the case of outbred species, inbreeding itself can be a welfare risk. Increased knowledge of livestock genomes will enable in vitro assessment of potential insertional mutagenesis and transgene instability. Characterization of the transgene sequence and flanking DNA regions of founder animals will provide insight into chromosomal location and the functionality of the flanking DNA, as well as the number and orientation of the inserted sequences. As the knowledge of animal genomes grows, such an in vitro analysis could provide a decision on whether to proceed with any further breeding of founder animals, saving resources and avoiding animal welfare issues that could arise if descendants were inbred to homozygosity, only then to identify a transgene-associated insertional mutation.

Freedom from insertional mutations and compatibility with production systems are essential for economic success and producer acceptance of transgenic livestock. Livestock producers want and expect trouble-free animals. The recent history of beef production in North America has demonstrated this fact. Breeders of the beef cattle breeds introduced from continental Europe during the 1970s have placed extraordinary emphasis on selection of these breeds for "convenience traits" such as reduced calving difficulty, increased fertility, and improved docility necessary for adaptation to extensive management conditions (Anderson, 1993). Livestock breeding is and will continue to be a balancing act of multiple trait selection; whether one favors or opposes genetic modification, it is naive to believe that transgenes will become so important as to monopolize selection practices.

Sources of Transgenes. Transgenic livestock animals developed for pharmaceutical production may ultimately incorporate transgenes from many sources, including the human species. Such animals are not intended or destined for the human food chain and will be subject to regulatory oversight by the U.S. FDA throughout the biopharmaceutical development and production process, including disposal. Presently, disposal of transgenic livestock by any means other than incineration or burial requires approval of an Investigational Food Additive application by the U.S. Food and Drug Administration.

In contrast, for transgenic food-producing animals to be acceptable to consumers, it seems fundamentally

important to avoid gene sources that create wrenching perception issues about food, or offend religious sensibilities. Transgenes originating from the same food animal species, or of synthetic origin, would seemingly create the fewest concerns. Origins of transgenes are in every sense a food marketing issue, not one of product quality or safety, because humans have ingested DNA from many sources over millions of years without ill effects. However, dietary practices have a heavy cultural association that profoundly affects attitudes toward what is edible. Recent experiences of consumer attitudes toward genetically modified plants suggest such obvious potential lightning rods as genes labeled “human” or genes offensive to religious dietary proscriptions should be avoided, or introduced only after extensive market analysis and consumer education.

Many DNA sequences are highly conserved across species; is it even appropriate to apply a “species label” to such sequences? The primary distinction between genes transferred between livestock species and transfer of genes composed of specifically human sequences is ethical. What degree of perceived humanization of a food animal is acceptable? From regulatory and right-to-know perspectives, cross-species transfer of genes may lead to labeling requirements or standards sufficient to satisfy the sensibilities of religious or other ethically based dietary practices.

Integrity of Species

“It is important to realize at the outset that terms such as species, subspecies, race and strain are man’s attempts to divide what is essentially a continuum of genetic change into an arbitrary series of discrete stages” (Short, 1976).

Within the span of a human lifetime, species may seem immutable, but there is indisputable molecular and cytogenetic evidence that they are not. For example, retroviruses seem to have had a major role in transferring DNA among the genomes of species throughout evolutionary history (Agrawal et al., 1998). Within even the period of a few years, humans can profoundly change domesticated species through applied selection. Within historical time, conventional methods of animal breeding have created phenotypic differences within some domesticated species that have resulted in physical barriers to mating and reproduction sufficient to reproductively isolate subpopulations. Reproductive isolation can become the first step on the path to separation into a new species (Short, 1976). Environmental changes and animal movements brought about by human activities can and do drive natural selection in new directions.

As with the perception of what is edible, attitudes toward molecular manipulation of animals are being formed within the context of the prevailing cultural and ethical framework of society. Some members of industrialized society long for a simpler, more natural

world, or a greater regard for the biosphere, and regard molecular genetics as impermissible tinkering with nature. Obviously, the spectrum of attitudes toward animals, ranging from completely utilitarian beliefs to attribution of natural rights to all biota, profoundly influences acceptance of human-controlled gene transfers among animals.

The government of a modern democratic society is obligated not merely to accommodate the deeply held moral convictions of its citizens, but to treat them with respect. But these convictions... are usually held by minorities no more numerous than those who hold the opposite conviction. The task of governments cannot be to legislate or regulate by making these convictions the basis of law, but it is rather to pursue policies that can command something close to a reflective consensus (Nuffield, 1999).

A reflective consensus in society about genetically modified organisms has not yet formed. However, it seems entirely reasonable to believe that reflection upon the differences between domesticated and undomesticated species can only lead to the conclusion that human-controlled genetic manipulation of the former is irreversible and will continue to reshape these species to meet human needs, whatever selection technology may be employed. Domestication of plants and animals accompanied, if not caused, human cultural evolution from hunter-gatherer societies. Continued co-evolution of human society with the selective breeding and utilization of domesticated organisms is inescapable.

Like other activities of the human species, selective breeding of animals, whether traditional or molecular, will rise to its highest and best level when conducted upon a foundation of ethical principles. As one ethicist has written:

... the genetic engineering of animals is morally neutral, very much like the breeding of animals, or indeed, like any tool. If it is used judiciously to benefit humans and animals, with foreseeable risks controlled, and the welfare of animals is kept clearly in mind as a goal and a governor, it is certainly non-problematic and can provide great benefits. On the other hand, if it is used simply because it is there, in a manner guided at most only by considerations of economic expediency and ‘efficiency’ or by quest for ‘knowledge for its own sake’, with no moral thinking tempering its development, it could well substantiate the worst rational fears in ‘the Frankenstein thing’ (Rollin, 1986).

Genetic Evaluations to Support Regulatory Evaluation

Livestock genetic evaluation systems are operated by public and private sector entities (BIF, 1996; Wiggans, 1997). The essential elements for accurate progeny testing include random distribution of animals across envi-

ronments, which is commonly accomplished through distribution of semen, accurate animal identification, and timely and accurate measurement of performance data. Producers have confidence in these systems and are accustomed to using them. If data gathering for regulatory evaluation of transgenic traits can be conducted through an existing genetic evaluation system, it is logical to use that system, provided that animal identification and data integrity meet regulatory standards. These systems, which were designed to evaluate multiple traits, provide the best opportunity to evaluate both direct and pleiotropic effects of transgenes. Prior regulatory approval of target animal and product safety evaluations will be necessary for the distribution of gametes or animals for progeny test field trials to be conducted.

Testing for some kinds of transgene efficacy, such as constitutive disease resistance, could be better evaluated by means of designed natural or artificial challenge infection experiments. Short-term infection challenge trials can establish benchmarks for resistance. However, the expected lifelong presence of constitutive immunity should also enable more meaningful evaluation of the economic and biological evidence for disease resistance throughout the production life cycle for the species involved. This process would more closely resemble existing progeny testing, such as for heritable differences in somatic cell count in the milk of dairy cows, than it resembles typical drug or vaccine trials.

Performance and progeny testing within successive generations of transgenic lines are particularly well suited to guide the introgression of a transgene into a breeding population. Potential genetic interactions could become quite complex, including animals with varying numbers of transgene copies and differences in additive expression of non-allelic transgenes. Complexity approaching that of quantitative inheritance could result from interactions when lines possessing completely different transgenes are crossed. As such effects are measured through animal performance and progeny tests, marker-assisted selection strategies could be used to guide breeding strategy within populations containing several transgenes.

Target Animal Safety and Food Safety

A key component of a transgene construct is a tissue-specific promoter selected to ensure that expression of the transgene occurs in the desired tissue. In designing expression of biopharmaceuticals in milk, obviously most effort has been focused on optimizing expression in the mammary epithelium. Such mammary-specific promoters are well understood. Mammary expression is equally important in the design of novel dairy products and expression of proteins directed at mastitis control. Different tissue tropisms are desirable for other transgenes but have been studied in less detail.

The diversity of potential applications in agriculture will call for a greater variety of promoters that can

direct gene expression to the tissue of choice in the animal's body. Choice of promoter is critical: in some cases expression in tissues other than the ones targeted would be detrimental to the animal, so a promoter with tight control of expression is essential. An inappropriate promoter can be self-defeating: high expression of a herpesvirus thymidine kinase transgene in the testes of mice resulted in sterility (Braun et al., 1990). In other circumstances, such as when an immunoglobulin gene is expressed, the gene product is innocuous and widespread expression in the animal may be desirable. By virtue of their own health and productivity, "animals are important indicators of their own food safety" (Berkowitz, 1993). Unlike some food plants that produce toxic proteins, food toxicity has not been associated with the common domesticated animal species.

In all the potential regulatory pathways for transgenic livestock, acceptable target animal food safety and tissue composition data will require laboratory evaluations meeting standards of assay validation and other quality assurance requirements embodied in FDA's Good Laboratory Practices (GLP) regulations (21 CFR 58, 1999). Customers for food will be the ultimate judges of whether food safety of transgenic livestock has been adequately demonstrated. If laboratory standards equal to the scientific rigor and quality assurance of drug development and manufacturing help achieve consumer confidence, the commercial interests of all participants in the food chain will be well served.

Use of Selectable Markers

Selectable markers are genes encoding resistance to antibiotics or other cell toxins. These genes are included in a transgene construct for the purpose of enabling selection in the laboratory of those cells into which the construct has been transferred. Selection is made by identifying cells capable of surviving in growth medium in the presence of the antibiotic. Markers commonly used in selecting transgenic cells are enzymes that inactivate aminoglycoside antibiotics such as neomycin or kanamycin. Antibiotic resistance markers are most useful in molecular biology when the efficiency of transferring gene constructs is poor, and when a pool of many cells is targeted for transfection.

The U.S. Food and Drug Administration has issued a guidance document regarding the use of selectable antibiotic resistance marker genes and has approved certain antibiotic resistance marker genes as safe for use in several species of transgenic food plants. In preparing its guidance document, FDA and its advisory committee considered several objections to the use of these genes in food, including concerns that such resistance genes might be transferred to intestinal bacteria of persons or animals consuming food products produced from transgenic plants or animals (US FDA, 1998).

A commonly used resistance marker gene in molecular biology is aminoglycoside 3'-phosphotransferase II

(*kan^r*). Because of their potential to produce long-lasting tissue residues in livestock, the aminoglycoside antibiotics are rarely administered to those species. The FDA has not yet made a regulatory determination regarding the safety of antibiotic marker genes in transgenic food animals. The conclusion that prevailed in the FDA's previous evaluation of use of *kan^r* in certain transgenic plants was that degradation of the DNA, as well as the enzyme it encodes, by conditions of cooking and digestion is so profound as to make untenable the hypothesis of transference of resistance (US FDA, 1998).

Animal Identification

Transgenic livestock used for the production of pharmaceuticals must be acquired, managed, and disposed of by pharmaceutical manufacturers operating under FDA's current Good Manufacturing Practices (cGMP) regulations (21 CFR 210, 1999). Reliable animal history, identification, and chain of custody are intrinsic in the capability needed to trace pharmaceutical ingredients back to the animals that produced them and to retrieve the animals' complete health and production histories. Reliable identification is also essential to prevent such animals from entering the human food chain. Consequently, redundant individual animal identification, including devices such as implantable transponder chips, is a *sine qua non* of pharmaceutical production.

Transgenic food-producing animals are likely to become a significant new challenge to the effectiveness of existing systems of animal identification. Depending on the regulatory environment and market requirements for identification of raw and manufactured products, greater capacity for identifying and tracing the movement and disposition of such animals could become necessary. Unlike their conventionally selected peers, transgenic livestock incorporate an inherited "label" in the form of the transgene construct itself. Polymerase chain reaction technology is capable of quickly and accurately identifying specific transgene sequences, provided the correct DNA primers and appropriate quality assurance are employed. The very existence of transgenic technology will create a market for diagnostic tests for the presence of transgenes to be applied within the food processing chain. If such tests are considered to be assays of food composition, their use is very likely to fall under GLP regulations.

Trade and Environmental Dissemination

Although livestock occasionally become feral, their reproductive isolation has reduced the probability of interbreeding with wildlife species to a miniscule level. Unlike with plants, asexual reproduction and wind-borne dissemination of animal gametes does not occur. Unlike trade in plant seeds, which are easily stored and transported, transportation of animal gametes and embryos requires cryogenic storage. Because of these

differences, far fewer opportunities exist for livestock to transfer transgenes to ecologically competent, related species than is the case for plants.

Animals themselves can be identified in several ways, and transgenic tissues or the semen of transgenic males can be identified by genomic analyses. Animals devoted to pharmaceutical production, and presumably their gametes and embryos, are subject to significantly greater regulatory oversight than conventional livestock (USDA FSIS, 1994; USHHS NIH, 1996).

At this time, regulations for domestic and international trade in livestock germ plasm have given very little consideration to the existence of transgenic livestock, or the likelihood that such animals and germ plasm will enter trade. Of a number of international animal health regulations recently examined, only those of Australia even make reference to the possibility of trade in transgenic animals.

The period during which transgenic livestock technology is in its infancy would be an excellent opportunity for regulatory agencies to consider the suitability of present standards of animal identification and movement controls, and to begin discussing these policy issues with peer agencies and stakeholders.

Implications for Agricultural Marketing Practices

Preservation of Product Identity. Use of transgenic livestock can potentially create many new niches, and some major markets, for identity-preserved agricultural products that will be differentiated by the presence of transgene products. Existence of transgenic organisms can also create *de facto* niches for identified products that do not contain transgenes or transgene products. In effect, either the presence or the absence of transgenes has the potential to add value, provided demand is sufficient to support preservation of product identity.

In the case of animals destined for the meat trade, identity preservation will require reliable animal identification systems and point of slaughter or point of processing tests for the transgenes of interest. Certain practices already developing in the meat industry, such as carcass value grid-based marketing of beef cattle, value-added labeling, and expanding collection of carcass data for genetic evaluation systems, already depend on maintenance of product identity and will be synergistic with marketing practices for transgenic livestock.

For products such as milk or eggs that become separated from the source animals, identity is more likely to be based on identifying premises of origin and development of segregated transportation and processing. Some transgenes will be closely held. In such cases, it seems likely that integrated production and marketing systems will be the means through which product identity and marketing advantage will be secured.

Labeling. The recent acceptance by the United States and other exporters of agricultural commodities of the

principle that an importing nation may require certification that an agricultural commodity is free of genetic modification denotes a major step toward segmentation and “de-commoditization” of agricultural markets. The pathway ahead could prove to be contentious as the market practices and regulatory oversight necessary to implement labeling are developed. Overriding these developments will be the question “Who pays for labeling and product segregation?” Labeling is scarcely a problem for new products having intrinsic value to producers and consumers. However, labeling becomes progressively more onerous when applied to products that are truly commodities and include no vestiges of transgene DNA or protein. Examples of the latter would be butter oil or animal fat remaining from the milk or tissues of a transgenic cow. This issue has been framed very well:

A further question is the extent to which the consumer’s right to choose implies duties on producers over and above the duty to label. If all brands of some processed foods now contain GMO soya, the consumer of these foods is faced with Hobson’s choice. The right not to consume GM foods has little meaning when there are no non-GM foods to be consumed in their place, or no way of knowing which is which. But does the consumer have the right to buy a range of non-GM products that other people would not otherwise have chosen to produce?

To claim a right is often contentious. The point of claiming rights is to limit other people’s freedom. When we have a right, what other people may and must do is fixed by that right.

Claiming a right to have a product made available when the market would not otherwise have supplied it presents grave difficulties. It is one thing to insist that suppliers guarantee not to poison the consumer; it is another to insist that companies should supply any particular range of products. It is yet another to require that such measures should be accomplished at no cost to the consumer (Nuffield, 1999).

Where political, market, and trade forces drive the issue of labeling remains to be seen. It is clear that those transgenic livestock products having clearly demonstrable benefits for both producers and consumers will have the best political and market fundamentals behind them as the labeling issue evolves.

Patent Regulation. The U.S. Supreme Court has determined that genetically modified organisms are patentable subject matter, so long as the organism is new, useful, and non-obvious (USPQ, 1980). It held that microorganisms were patentable, and in so holding, quoted from Congressional committee reports and stated that “Congress intending statutory subject matter to include ‘anything under the sun that is made by man’.” This ruling has been extended to apply to genetic

modification of other organisms, such as plants, mice, and livestock.

The European Union, through Directive 98/44/EC, has extended the possibility of patent protection to biotechnological inventions (EPC, 1998). This directive provides that inventions of biological material, such as plants or animals, are patentable if such inventions are novel, imply inventive activity, and are capable of industrial application. A patent holder is permitted to prohibit the use of patented, self-replicating material in situations analogous to those in which the holder would be permitted to prohibit use of patented, non-self-replicating material. This directive distinguishes between a plant or animal “variety” and modifications of plant or animals characterized by particular gene(s). In the case of varieties, patents are not allowed, because a variety is characterized by its entire genome and is clearly distinguishable from other varieties. On the other hand, a grouping that is characterized by a particular gene, and not the entire genome, is patentable, because it is not covered by current legal protection.

Directive 98/44/EC specifies that genetic modifications of animals that are likely to cause suffering, without any substantial medical benefit in research, diagnosis, or treatment of animal or human diseases, may not be patented. It further provides an important derogation to farmers. Farmers are entitled to propagate a protected invention for further multiplication on their own farms. Only a fee similar to that permissible under plant variety rights legislation can be charged, and the farmer is entitled to use the “product of his harvest for further multiplication or propagation on his own farm.” The directive defers to national laws, regulations, and practices with respect to the extent and conditions of the farmers’ derogation, because there is no pertinent EU legislation on animal variety rights.

Testing for the Presence of Transgenes. Development and implementation of testing procedures for the presence of transgenes and(or) their products are linked to the interests of all those involved, from developers of the intellectual property to the consumers of foods. Because of the multiplicity of interests involved, application of tests is likely to be frequent, and such tests may range from field application of “quick tests” to sampling in regulatory or other laboratories for oversight purposes, requiring extensive quality assurance precautions and accounting for chain of custody.

Whereas the use of PCR to identify a DNA sequence can be extremely sensitive, use of the method requires quality assurance to avoid spurious results. Unless test validation standards are agreed to by the trading community, testing for transgene sequences could become a chaotic mix of many laboratories and methods. Use of differing primer sequences, lack of laboratory quality assurance, or application of inconsistent methods by vendors and customers could easily become barriers to international trade.

Development of standard testing methodologies and DNA primer sequences for specific transgenes will be

fundamental to orderly markets and regulatory oversight. Application of GLP standards requirements, as applied by the FDA to regulation of the pharmaceutical and food industries, should meet several essential requirements of public interests (appropriate regulation and fraud prevention) and private interests such as dependable market access and protection of intellectual property (21CFR58, 1999). For orderly, science-based world trade to continue, the technical standard setting that has been delegated by the World Trade Organization to Codex Alimentarius, the International Office of Epizootics, and the FAO International Plant Protection Convention will need to encompass testing methodologies for genetic modifications.

Requirements for testing could be incorporated into bilateral zoosanitary and phytosanitary agreements for trade in animals, plants, and germ plasm. This will require expansion of the laboratory and regulatory oversight competence of the agencies that make or endorse trade certifications.

Impact of Transgenic Livestock on USDA Regulatory Programs

This discussion is not intended to support or oppose regulation of transgenic livestock by USDA or any other agency. It is intended to describe where some potential activities could overlap activities historically a part of USDA regulatory programs. Some of the activities identified are not USDA programs, but interface with them.

Animal Identification. Transgenic livestock are among several converging developments increasing an already urgent need for an effective, integrated national animal identification program, one that is freely and rapidly accessible by all relevant public and private sector interests. To the extent the regulatory pathway for approval of transgenic livestock resembles the New Animal Drug process, once initial target animal and food safety approval is received, field trials for the purpose of evaluating transgenic livestock could then begin. If identification of field trial animals can be accomplished within the existing identification system, creation of another isolated identification database of transgenic livestock would be a bad precedent, because further fragmentation would only weaken a system already diffused among many entities and objectives. The lack of utility of isolated databases of identified animals is exemplified by breed herdbooks, which identify a small minority of agricultural livestock and have an insignificant role in identifying the 'non-purebred' offspring of herdbook animals.

It remains to be seen whether New Animal Drug regulation can deal with self-replicating entities (animals) throughout the process of introgression of transgenes into the national herd. Setting this uncertainty aside momentarily, the policy raises the prospect of a larger role for the FDA in some aspects of livestock breeding, identification, and evaluation. Wherever the ultimate regulatory oversight of transgenic livestock

comes to rest, the FDA and USDA should be coordinating many aspects of policy development, including animal identification systems, database maintenance, and tracing of movement. In evaluation of transgene-mediated disease resistance, coordination of regulatory oversight responsibilities between the USDA APHIS Veterinary Biologics and the FDA will be necessary.

Disease Eradication Programs. Considering the time required for development of transgenic livestock, an immediate impact on existing national animal disease eradication programs is unlikely. Eradication of brucellosis and pseudorabies has progressed sufficiently to support prediction that both diseases will be gone from the United States before transgenic livestock become common (Hagerty et al., 1999; Ragan et al., 1999).

The potential for constitutive expression of disease resistance by transgenic livestock does suggest that such animals could be employed in eradication or control of some currently prevalent infectious diseases. If the public health or other interests demand that new eradication programs take on complex or enzootic livestock diseases, then transgenic disease resistance should be considered as a potential tool in such programs.

The potential for transgenic livestock expressing one form or another of constitutive disease resistance will make it necessary to adopt official diagnostic tests that are compatible with whatever forms of resistance might ultimately be engineered into transgenic livestock. The logic of developing widespread competence by official diagnostic laboratories in molecular identification of animals' genotypes is inescapable. As a matter of regulatory policy, it may be prudent to think through the implications of a relationship wherein the developer or owner of a particular livestock transgene is also the marketer of a proprietary diagnostic test to regulatory laboratories. If the FDA remains involved in this arena, its quality assurance requirements will become much more important within the sphere of animal diagnostic laboratories.

Domestic and International Movement of Livestock and Germ Plasm. If the mobility of transgenic livestock within the national herd were restricted in any significant sense by regulation, oversight of movement controls would most logically fall to the state and national animal health agencies that currently regulate livestock movements. It is difficult to envision any other agency developing a parallel infrastructure for this purpose. As in the areas of animal identification and diagnostics, transgenic livestock seem to bring the FDA and USDA responsibilities closer together.

There is presently no significant USDA regulatory oversight of domestic movement of livestock germ plasm. The artificial insemination and embryo transfer industries have been self-regulating in every respect except where their activities overlap with the requirements of official disease eradication programs and they need to obtain USDA export animal health certifications. It is not even clear that statutory authority for

regulation of these industries exists, beyond the limited scope of current disease eradication activities and regulations for interstate movement of animals.

Similarly, it is not clear that USDA, under its present authority, could regulate importation of transgenic livestock or germ plasm from transgenic animals under any authority other than the disease control provisions currently found in Chapter 9, Code of Federal Regulations (**CFR**). Those provisions, in Parts 93 and 98 of 9 CFR, do not make reference to animal genotypes. In the case of exports, the situation is not at all clear. In the past, the USDA has been reluctant to negotiate export animal health certification protocols with importing nations that include certifications about animals' ancestry or genetic characteristics, preferring to leave genetic certifications within the scope of commercial agreements between traders. From a policy standpoint, it is arguable whether certifying accredited veterinarians or endorsing USDA veterinarians can reasonably attest to characteristics such as transgenic status. Nevertheless, by its compliance with the recent Biosafety Protocol to the United Nations Convention on Biological Diversity, the United States recognizes importing nations' right to require information about genetic modification as a part of import requirements for plant and animal genetics. If not incorporated into the animal health certifications, how will information about genetic modification of livestock be provided?

The constructs, stem cells, and vectors used to create transgenic animals will come to be traded internationally. The distinction between *in vitro* and *in vivo* applications of these biological preparations will blur as DNA sequences are moved around the world or are simply synthesized where needed from published sequence information for the purpose of livestock research and development. Highly efficient vehicles for gene transfer may be created in one part of the world and shipped elsewhere, in order to transfer genes into indigenous livestock. Stem cells originating in one part of the world could be shipped to another location for transfection with DNA, and to yet other locations for nuclear transfer or storage. Just as with the well-characterized oversight of international trade in semen and embryos, regulatory attention will be necessary to ensure that contamination by adventitious agents or misrepresentation of the identity and potential use of DNA sequences does not occur.

As noted previously, there are significant implications for the USDA's need to develop expertise in the analysis (diagnosis) and interpretation of animal genotypes, based on molecular diagnostic techniques, if it is to become a credible regulator in this arena.

Records of Ancestry. In the conventional livestock breeding industry in the United States, records of ancestry of purebred animals are kept by private sector breed associations. In Canada, many records are kept on behalf of breed associations by the Canadian Livestock Records Corporation (**CLRC**), a quasi-public corporation incorporated under the Animal Pedigree Act,

which is national legislation regulating the keeping of animal pedigree records in Canada. The CLRC maintains voluntary records of ancestry and identification for non-purebred livestock animals, as well as animals of non-livestock species, and provides registration and access on the Internet (CLRC, 1999).

Transgenic livestock applications will cut across breed boundaries and could lead to formation of herdbooks maintained and controlled by the developers of the transgenic strains. Although records of ancestry are important to all breeders of livestock, it is records of identification and ownership that are of most value in animal disease control and food safety surveillance. As noted before, the key public interest in this area will be served by an openly accessible animal identification system that is not fragmented or controlled by any minority interest. In this context, public and private sector interests would do well to investigate automated, state-of-the-art livestock recording and identification systems such as the one maintained in the Netherlands by NRS, the Royal Dutch Cattle Syndicate. This system serves the needs of animal health, performance testing, and records of ancestry from a single database, and includes these elements (NRS, 2000): each bovine animal is tagged with an identification number only once; each animal and premises are identified by a unique number, including a control digit; identification is done with ear tags in both ears, including a bar code; animals are entered into an automated database shortly after birth; entry serves as certification for animal health and herd book registration; all movements of animals are recorded; producers enter newly acquired animals, using automated telephone or computer; and the system is closed, enabling all animals to be traced.

Unified Regulatory Oversight: An Attainable Goal?

The complexity of molecular animal breeding technology allows plausible arguments to be made for regulatory oversight by several agencies. From the viewpoints of producers of these animals, to say nothing of consumer confidence, fragmentation of regulatory oversight is undesirable. Such oversight should be appropriate to the characteristics of the technology. Canada, where food safety and animal health regulatory responsibilities are unified in the Canadian Food Inspection Agency, has been able to initiate a comprehensive process of consultation with all stakeholders about many of the regulatory policy implications surrounding transgenic livestock (CFIA, 1999).

The process of consultation itself could prove to be useful in defining where regulatory responsibility for transgenic livestock should ultimately be placed. The high degree of public interest in the application of genetic modification technology may prove to be a sufficient reason to provoke redefinition of the missions, structures, and the expertise of the responsible regulatory organizations.

Whether it is unified or divided, a clear and appropriate regulatory pathway for oversight of transgenic livestock technology is badly needed. Otherwise, development may be stifled, and public confidence damaged, by the failure of regulation to keep pace with scientific innovation. For government to become a credible leader in providing information that will help to achieve a reflective consensus within society about genetic modification, government itself must fully understand all the implications of this technology for food production, the environment, public and animal health, and national food security.

Conclusions

The advances made in developing transgenic livestock for biopharmaceutical production and other biomedical applications are producing technical innovations that make agricultural applications progressively more likely. The possibility of transgenic livestock brings into focus issues pertinent to all livestock production and food safety regulation. Curtailed antibiotic use on farms and the potential for broad, low-technology disease control through genetic delivery of resistance are also important driving forces. The narrow margins of agriculture make it necessary for livestock producers to examine all the possible tools to produce healthy food economically.

Genetically modified livestock in agriculture are already an experimental reality and can rapidly become a commercial reality. Will the existing regulatory model work, and will the pathway be clearly defined? Will existing animal identification, animal tracking, and marketing practices be up to the challenge? The key test of regulatory policy and industry practices will be their capacity to build consumer confidence.

While the technology clock ticks, producers, consumers, and regulators have an opportunity to arrive at a "reflective consensus" about transgenic technology. The time available to forge such a consensus must be used productively by those who develop the technology, working and communicating with consumers, producers, and the regulatory agencies involved. A well-marked regulatory pathway for genetically modified livestock will build confidence and support development of a consensus, wherever it may lie.

Implications

Scientists engaged in the development of transgenic livestock intended to supply food must recognize that regulators and society currently regard gene transfer as a distinct departure from traditional animal breeding practices. In this environment, developers of transgenic technology should consider animal health and welfare and key societal concerns, such as environmental impact, food quality and safety, to be as important as enhanced productivity. Regulatory requirements for transgenic livestock are not yet definitive but clearly

have the potential to affect existing regulatory and industry practices in such important areas as animal health and diagnosis of disease, trade certifications, recording of animals' identification and ancestry, genetic evaluations, and product identity and traceability.

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