



Regulating Bioengineered Animals

Are We Ready?

by Robert B. Nicholas and Valentin A. Povarchuk

Humans began domesticating and artificially breeding animals more than 8,000 years ago.¹ Yet it was not until the 1960s that new molecular biology techniques presented the possibilities of rapidly modifying the genetic code to produce desirable traits in the organisms and the products produced by the organisms. In the 1970s, first the National Institutes of Health (NIH), and then more broadly the U.S. government undertook an effort to examine if and how the newer technologies and their products should be regulated.

The 1986 Coordinated Framework for the Regulation of Biotechnology (Coordinated Framework) remains the main federal policy statement on the jurisdiction of various agencies over biotechnology products.² The 20-year-old policy is based on the principle that the products of biotechnology should be regulated in a similar manner to the equivalent conventional products and the view that for the most part, existing laws adequately address the regulatory needs of biotechnology.

During the past two decades, the Food and Drug Administration (FDA)

has issued numerous guidelines and approved many human health related drugs, biological products, and *in vitro* diagnostic tests, as well as food enzymes, but notwithstanding various efforts over the past several years the agency has not yet issued guidance for the food use of transgenic animals. The regulated community believed FDA was close in the fall of 2005 when then Commissioner Lester Crawford announced that FDA would shortly be issuing a new policy.

Shortly before this article went to press, the FDA released Draft Risk Assessment, Risk Management Plan, and Industry Guidance regarding the safety of animal clones and their progeny for food consumption, finding that the meat and milk from clones of adult cattle, pigs, and goats, as well as their offspring, are safe to eat as food. However, this draft guidance specifically excludes genetically engineered animals. FDA will consider public comments received by April 3, 2007, but given the amount of



controversy surrounding this issue, a final policy may not be available for a long time.

Increased Animal Biotech

“Modern” genetic engineering involves a series of scientific techniques used to modify an organism’s genome by introducing new genes, creating what are known as “genetically modified organisms” and in the case of animals “transgenic animals.”³ The potential applications of animal biotechnology are numerous and varied. Laboratory rats, mice, and rabbits have been genetically modified to mimic human diseases and are now commonly used for medical research.⁴

More recently, scientists have developed transgenic animals



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capable of producing large amounts of therapeutic proteins in their milk at relatively low cost.⁵ The proteins can then be purified and used to treat human and animal diseases. The shortage of human organs for transplantation has led scientists to explore xenotransplantation, a biotechnology by which the organs of animals (usually pigs) are genetically modified to minimize the transplantation risk of rejection. To date, neither of the latter two applications of transgenic animals has been approved for human use, although the technique for production of alpha-1-antitrypsin, a human blood protein used to treat hereditary emphysema, cystic fibrosis, and chronic obstructive pulmonary disease, is undergoing clinical trials in Europe.⁶

Of special interest for the purposes of this review is the unexploited application of transgenic animals for human food production. So far, the best-known example of this application is the creation of a fast-growing species of Atlantic salmon. To breed large transgenic mammals—cows or pigs, for example—scientists combine two techniques: first they create the transgenic animal with the desired characteristic (e.g., leaner, faster growing, disease resistant) by inserting new genes into the animal's genome, and then use cloning to create replicas to produce a core breeding herd.⁷ Regulators have requested that the developers of such transgenic animals refrain from releasing food products derived from these animals or their progeny into the market to allow for the assessment of potential risks.⁸

Regulation of Transgenic Animals

Decisions regarding the introduction

of various products of animal biotechnology rest with several U.S. government agencies with different and sometimes overlapping jurisdictions, and sometimes more than one agency may be involved in the approval process.⁹ Under the Coordinated Framework, jurisdiction over the varied biotechnology products is determined by their use, as has been the case for traditional products.¹⁰ FDA's Center for Veterinary Medicine (CVM) has claimed broad jurisdiction over transgenic, genetically modified, and cloned food animals and fish, meat, milk, eggs, and other edible food products derived from them; as well as animal drugs from genetically modified animals (biopharm animals).¹¹

CVM has indicated that it will regulate transgenic animals and their products using the "new animal drug" approval provisions of the Federal Food, Drug, and Cosmetic Act (FDCA).¹² An early articulation of this position is found in a 2001 government report (CEQ/OSTP Case Studies), which concluded that the genetic constructs inserted in animals, and their expression products are "drugs."¹³ The stated rationale for this position is that the genetic constructs as well as the proteins they produce are "drugs" because they necessarily "affect[] the structure or any function of the body of man or other animals" within FDCA's meaning of the term.¹⁴ Using the same reasoning, CVM also asserts jurisdiction over progeny of genetically modified animals when they inherit genetic constructs inserted into parent animals.

The natural consequence of this position is that field investigations will require an investigational new animal drug application (INAD) and approval of the new animal drug application will

require the sponsor to demonstrate both 1) the "drug's" safety with respect to the target animal, and 2) human food safety with respect to consumption of the edible portions of these animals.¹⁵ For the purposes of human safety, this means that any residue of the animal drug must be at or below a level that, when the animal is consumed, results in a reasonable certainty of no harm.¹⁶ CVM has also interpreted its animal drug authority as allowing it to consider environmental effects of transgenic animals.¹⁷

Transgenic food animals sometimes may also fall within the regulatory authority of the U.S. Department of Agriculture's (USDA's) Animal and Plant Health Inspection Service (APHIS) and Food Safety and Inspection Service (FSIS). APHIS administers the Animal Health Protection Act,¹⁸ the Plant Protection Act,¹⁹ and Animal Damage Control Act,²⁰ all of which may apply to genetically engineered animals in certain circumstances. Most significantly, the Animal Health Protection Act may provide APHIS with authority to regulate "environmental release" of transgenic animal livestock out of concern for livestock disease and pests, as well as some other environmental concerns.²¹

FSIS serves as the final gatekeeper to the marketplace for meat and poultry products under the Federal Meat Inspection Act²² and the Poultry Products Inspection Act.²³ In this role, FSIS inspects meat processing facilities and most types of animals offered for slaughter ante- and post-mortem, to ensure that meat is not adulterated or misbranded. Since food is deemed adulterated if it exceeds certain levels of environmental contaminants or food additives, FSIS's meat inspection



program enforces food safety standards and decisions of the FDA and Environmental Protection Agency (EPA).²⁴ So far, the USDA also has not issued any guidance as to how it intends to apply any of its authorities to the regulation of transgenic animals.²⁵

A Range of Concerns

Over the past decade various expert groups have met, public meetings have been held, and reports written exploring the range of legal, scientific and ethical concerns about the development, use and regulation of transgenic animals. For example, the 2002 NRC Study and 2004 Pew Report have raised several important issues about CVM's assertion of jurisdiction under new animal drug authority over transgenic animals created for human consumption.

First, assuming that regulating genetic constructs and their expression products as "drugs" is a fair reading of the FDCA's definition of the term

"drug," transgenic animals do not easily fit within the CVM regulatory scheme for new animal drugs. For example, regulations governing drug labeling, good laboratory practices, and good manufacturing practices do not seem readily adaptable in the context of transgenic animals.²⁶

Second, CVM's jurisdiction over progeny of animals created by genetic engineering has been questioned. An extension of FDA's authority from the initial transgenic or cloned animal to subsequent generations requires that the subsequent generations be considered as "intended" modifications of the structure or function of these animals.²⁷ While there is some support for such an interpretation,²⁸ the determination of intent would likely depend on the facts of each specific case.²⁹ Regulating the offspring of transgenic animals can also become a slippery slope of subjecting each subsequent generation of offspring to regulation in perpetuity because each

generation will inherit the same genetic construct. Clearly any CVM policy will need to deal with this matter and it can do so by relying on FDA's food additive authority.³⁰

Third, CVM's assertion of jurisdiction to evaluate environmental effects of transgenic animals also stretches the limits of its statutory authority. FDA's authorizing legislation has no statutory standard for making regulatory decisions about environmental risks, and the agency has acknowledged that it does not have authority to consider environmental impacts that do not raise human or animal health issues.³¹

Finally, in the absence of formal guidance or regulations from CVM about the extent of its jurisdiction over food products obtained from transgenic animals and how it plans to exercise it, the confidential nature of the new animal drug approval process has become for some a cause

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for concern. Under the current law, CVM must keep the existence of an application for approval of a new animal drug confidential.³² While this helps to protect intellectual property of the new animal drug sponsor, the lack of transparency and opportunity for public comment can only inhibit public acceptance of already controversial animal biotechnology products.³³

Although FDA's mandate undoubtedly provides it with authority to regulate food derived from transgenic animals, it is not clear how far the regulation can be extended, and it's questionable whether it can extend to environmental assessments. In addition, other agencies may have concerns that FDA cannot address—for example, USDA's concerns about livestock safety and animal pests.

In addition to the legal uncertainty regarding CVM's assertion of jurisdiction and the practical problems of implementing such a scheme, transgenic and cloned animals for food use have raised and continue to raise for some ethical, animal welfare, and similar social concerns. Further, the possibility exists that our trading partners in Europe and Asia will react negatively to transgenic animal food products, much as they have to transgenic crops generally, and in particular to inadvertent genetic transfer from unapproved varieties of transgenic corn—and, more recently, rice—to non-transgenic crops intended for export.

In light of ongoing regulatory uncertainty, the agencies need to coordinate their authorities to determine appropriate roles and responsibilities and publish a clear road map. However, the distrust most Americans feel toward food produced by transgenic animals may make it more difficult to propose a new regulatory policy. Additionally,

the recent shift in the majority control of Congress, with expected additional oversight of FDA, means that any new policy is likely to undergo careful scrutiny.

Conclusion

The inexorable advent of biotechnology into the field of genetic engineering of food animals has the potential to enhance the production of human and animal food. While the principal U.S. regulatory agencies responsible for approving new products derived from transgenic animals do not seem intent on preventing the development of animal biotechnology-derived products, they do not appear to be equally prepared for what is to come either.

In particular, FDA has yet to deal with many issues of the regulation of food products of transgenic animals. With decisions regarding the marketing of the meat and milk of transgenic animals looming in the near future, FDA and other agencies need to formally clarify their regulatory approaches and the basis of their jurisdiction for evaluating animal biotechnology products. Further, extension of FDA's jurisdiction to animals bred from transgenic parents and authority to review potential environmental impact of transgenic livestock may require express Congressional authorization. ▲

- 1 National Research Council, *Animal Biotechnology: Science Based Concerns*, NATL. ACADEMIES PRESS, (2002) 4 (NRC Study).
- 2 Coordinated Framework for Regulation of Biotechnology; Announcement of Policy and Notice for Public Comment, 51 Fed. Reg. 23,302 (June 26, 1986) (Coordinated Framework).
- 3 A useful diagram for understanding the process of creation of transgenic animals is provided in Carol Lewis, *A New Kind of Fish Story: The Coming of Biotech Animals*, FDA CONSUMER, (Jan.-Feb. 2001).

- 4 See Lester Crawford, *Genetic Kingdom: Reaping the Bounties of Our Biotech Future*, THE AMERICAN ENTERPRISE (Mar. 2004) 22.
- 5 See Randy Vines, Virginia Cooperative Extension, *ANIMAL BIOTECHNOLOGY*, Pub. no. 443-003 (2002) for list of proteins with therapeutic and industrial value that have been produced, but not commercialized, in the milk of transgenic animals.
- 6 Crawford, *supra* note 4, at 23.
- 7 Lewis, *supra* note 3, at 19.
- 8 Vines, *supra* note 5; Crawford, *supra* note 4, at 23.
- 9 Vines, *supra* note 5.
- 10 *Id.* at 23,304.
- 11 CVM, *Food Safety Evaluation of Transgenic Animals*, FDA VETERINARIAN NEWSLETTER, Mar./Apr. 1996; *Draft Guidance for Industry 153: Drugs, Biologics, and Medical Devices Derived From Bioengineered Plants for Use in Humans and Animals* (Sept. 2002), both documents available at http://www.fda.gov/cvm/bio_drugs.html (last visited Nov. 25, 2006). Generally, drugs for human use produced by transgenic animals, including biological products, are regulated by FDA's Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER).
- 12 *Id.*; PEW INITIATIVE ON FOOD AND BIOTECHNOLOGY, *Issues in the Regulation of Genetically Engineered Plants and Animals* (Apr. 2004) 113, available at <http://pewagbiotech.org/research/regulation/> (last visited Nov. 29, 2006) (Pew Report); 21 U.S.C. § 360b.
- 13 Pew Report at 102, 104; Case Study One: Salmon plus sidebar, CEQ/OSTP Assessment: Case Studies of Environmental Regulation of Biotechnology (2001) 13, available at <http://www.ostp.gov/html/012201.html> (last visited Nov. 29, 2006) (CEQ/OSTP Case Study).
- 14 CEQ/OSTP Case Study at 13; 21 U.S.C. § 321(g)(1)(C).
- 15 See 21 U.S.C. §§ 360b(d)(1); 321(u).
- 16 See 21 U.S.C. §§ 360b(a)(1); 21 C.F.R. § 570.3(i).
- 17 Pew Report at 111.
- 18 7 U.S.C. § 8301 et seq.
- 19 7 U.S.C. § 7701 et seq.
- 20 7 U.S.C. § 426.
- 21 Pew Report at 105.
- 22 21 U.S.C. § 601 et seq.
- 23 21 U.S.C. § 451 et seq.
- 24 Pew Report at 117-118.
- 25 *Id.* at 105; however, USDA has issued guidance on regulation of insects that are "plant pests." See 7 C.F.R. Part 340.
- 26 Pew Report at 120.
- 27 *Id.*
- 28 See 21 C.F.R. § 201.128 (providing that the words intended uses refer to the objective intent that may be demonstrated by circumstantial evidence); *Agnew v. United States*, 165 U.S. 36, 53 (1897) ("the law presumes that every man intends the legitimate consequences of his own acts").
- 29 Pew Report at 121.
- 30 FDA regulates the safety of food additives under 21 U.S.C. § 342(a)(1). However, a substance added to food is not a food additive if it is "generally recognized as safe" (GRAS). 21 U.S.C. § 321(s).
- 31 CEQ/OSTP Case Study at 14. See also NRC Study at 114.
- 32 See 21 U.S.C. § 331(j).
- 33 Pew Report at 125.